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**Roland Collicott CChem MRSC**

**Investigation of Chiral Silicon Compounds for the Determination of  
Enantiomeric Purity**

**Submitted for the degree of PhD in chemistry. 31 December 2001**

**Study based at the Open University in collaboration with  
Hoechst Roussel UK Ltd and the Royal Society of Chemistry (Analytical  
Chemistry Trust Fund SAC Research Studentship)**

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## ABSTRACT

Over the past two decades, chiral synthesis and separation have grown in importance, particularly in pharmaceuticals, where gross differences in pharmacological behaviour can occur between the enantiomers of a compound. The most tragic example is that of the racemic sedative, thalidomide. Widely used by pregnant women in the 1960's, it was the cause of deformity in many of their children. Under certain circumstances, only the *S*-(-)-enantiomer produces the teratogenic effect.

The search for specific information on the effects of different enantiomers and increasing attempts to prepare enantiomerically enriched compounds has led to a large demand for enantioselective analytical methods. The two most widely employed techniques are NMR spectroscopy and chromatography.

My research at the Open University focused on reagents based on silicon which could be used for derivatisation with the facility of the ubiquitous trimethylsilyl (TMS) reagents. I have investigated chiral chlorosilanes, in racemic form, to derivatise nucleophilic analytes. Because of the symmetry properties of some of the chiral silicon reagents prepared, the stereochemistry of the products is not dependent on the mechanism of reaction between an analyte and the reagent.

The reagents were assessed by derivatising three chiral alcohols, which were used as model analytes: (1*R*, 2*S*, 5*R*)-menthol, 2-octanol and 1-phenylethanol. Chloromethylphenylsilane produced derivatives that were well resolved by GC, but was considered a poor choice of reagent on the grounds of its instability to racemisation and the instability of the diastereoisomeric products. 1-Phenylethylchlorodimethylsilane gave derivatives that were well distinguished by NMR, while only partial separation by HPLC was obtained from the 2-octanol and 1-phenylethanol derivatives. No GC separations were achieved from this reagent. Two reagents possessing pseudo- $C_2$  symmetry, bis(1-phenylethyl)chloromethyl-

silane and 1-chloro-1-methyl-2,5-diphenylsilacyclopentane were also unsuccessful in GC analysis, but the latter provided some promise for NMR analysis, with the derivatives of menthol being particularly well resolved.



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## LIST OF ABBREVIATIONS

$\alpha$	separation factor <sup>1</sup>
amu	atomic mass units
CD	circular dichroism
CDR	chiral derivatisation reagent
CE	capillary electrophoresis
CEC	capillary electrochromatography
CIMS	chemical ionisation mass spectrometry
COSY	Correlation Spectroscopy (in NMR)
CMP	chiral mobile phase
CSA	chiral solvating agent
CSP	chiral stationary phase
CSR	chiral shift reagent
d	doublet (NMR)
DCM	dichloromethane
DEPT	Distortionless Enhancement by Polarisation Transfer (NMR)
diast	diastereoisomer
EIMS	electron ionisation mass spectrometry
FID	flame ionisation detector

FTIR	Fourier transform infrared
GC	gas chromatography
GC/MS	gas chromatography with mass spectrometric detection
h	hours
HPLC	high-performance liquid chromatography
IR	infrared
m	multiplet
min	minutes
mmu	milli atomic mass units
mol	mole
MS	mass spectrometry
m/z	ratio of relative molar mass / charge
NMR	nuclear magnetic resonance spectroscopy
q	quartet
RA	relative abundance
$R_s$	peak resolution <sup>1</sup>
s	seconds / singlet (NMR)
t	triplet
$t_{1/2}$	half life

$t_M$	hold-up time (chromatography) <sup>1</sup>
$t_R$	retention time <sup>1</sup>
TLC	thin-layer chromatography
TMS	trimethylsilane or trimethylsilyl
UV	ultraviolet

## **CHAPTER 1**

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# INTRODUCTION

## 1.1 THE NEED TO DISTINGUISH BETWEEN ENANTIOMERS

In 1848, working on tartaric acid from wine, Pasteur was the first to appreciate that biological systems exhibit stereoselectivity and that there was some dissymmetric force at work in nature.<sup>2, 3</sup> For instance, the enantiomers of tartaric acid were decomposed at different rates by moulds or yeasts, so that the optical rotation increased as a racemic solution became depleted in one enantiomer.<sup>4</sup> The first recognition of differences in the biological effects of enantiomers was in 1886 when Piutti<sup>5</sup> found that one enantiomer of asparagine tasted sweet, while the other tasted bland. That enantiomers of a given chiral compound have different pharmacological activity appears to have been demonstrated first in 1904 by Cushny.<sup>6</sup> Cushny carried out a number of experiments on the autonomic nervous system, which included measuring the amount of drug necessary to elicit the same response on the dilation of the pupil of the eye, or the inhibition of salivary secretion. He demonstrated that (-)-atropine was twice as active as the racemic form. Many papers on the subject of enantiomeric drugs have since been published, and the significance of stereochemistry in biological systems is now better understood.

Differing biological properties between enantiomers may occur if there are differences in absorption, distribution metabolism or excretion (ADME) and/or discrimination at the receptor level, *i.e.* enantioselective pharmacodynamics.<sup>7</sup> It is hardly surprising that, for example, receptor sites or enzymes, having such well defined stereochemistry, often exhibit marked differences between their interactions with enantiomers. The consequences of this can be as tragic as those caused by the racemic drug, thalidomide. In Europe, this drug, a sedative and anti-emetic, was allowed for use during pregnancy and resulted in serious birth defects. Only the *S*-(-)-enantiomer of this drug was later found to be teratogenic to rats and mice following intraperitoneal application,<sup>8</sup> leading many to believe that the



tragedy could have been averted had the *R*-(-)-enantiomer been used. That this conclusion is definitely valid was queried in 1989 by de Camp of the US Food and Drug Administration (FDA).<sup>9</sup> Subsequent research in 1994 showed that, although fairly stable to racemisation in phosphate buffer at pH 7.4, either enantiomer of thalidomide was rapidly racemised in human plasma ( $t_{1/2} < 12$  min),<sup>10</sup> which would definitely lead one to presume that administration of the *R*-(-)-enantiomer of thalidomide would not be a safe option. Research into thalidomide has continued because it has potential for the treatment of other medical conditions. In a recent review it was stated that the *R* enantiomer is enzymically converted in the liver to the *S* enantiomer.<sup>11</sup> Generally, the fact that there can be a large difference in the teratogenicity of the two enantiomers in laboratory animals or human subjects emphasises the need to consider enantiomers as two distinct drugs.

There are a large number of compounds to which these considerations apply. A survey<sup>12</sup> of the pharmaceutical products on the market in 1993 showed that, of 1850 compounds available, 28% were of natural origin or were semi-synthetic, while 72% were synthetic. The vast majority of naturally-based compounds were chiral and were marketed as the naturally-originated homochiral product. Of the synthetic products, 40% were chiral, 88% of these (that is, 467 compounds) being sold as racemates. As pharmaceutical companies have concentrated on this area, the proportion of drugs marketed as single enantiomers has steadily increased: to 30% of a \$335bn total worldwide drugs market in 1998 and again to 32% of \$360bn market in 1999.<sup>13</sup>

Either enantiomer may be of therapeutic benefit (and to varying degrees) or have no effect, or may exhibit toxicity. For example, dextropropoxyphene is an analgesic, whereas laevopropoxyphene is an antitussive.<sup>14</sup> The reversed trade names of these drugs, Darvon and Novrad respectively, reflect their mirror-image relationship. Both enantiomers of timolol reduce intra-ocular pressure, but the *S* enantiomer is the more potent beta-blocker.

The *R* enantiomer is therefore the preferred choice for the treatment of glaucoma, since the systemic side-effects are reduced.<sup>15</sup> The dextrorotatory enantiomer of ketamine is predominantly hypnotic and analgesic, while the laevorotatory enantiomer is the main source of unwanted side effects, such as CNS-stimulatory activity.<sup>16</sup> Thal<sup>17</sup> lists 15 common chiral drug compounds, the enantiomers of which have different pharmacological effects, and this list is by no means exhaustive.

The implications of administering a racemate are clearly quite involved. The complex pharmacological considerations of using homochiral, racemic or even other proportions of enantiomers was reviewed by Ariëns<sup>18</sup> and de Camp.<sup>19</sup> Affiliated to the US Food and Drug Administration (FDA), de Camp's message of concern was amplified in 1993 when he stressed the FDA requirement for either or both a stereochemically specific identity test and a stereochemically selective assay method.<sup>20</sup>

Over the last ten years, many major pharmaceutical companies have changed philosophy and switched to a policy of developing homochiral or achiral drugs. There is also a lucrative market in homochiral versions of compounds currently sold as racemates, on the basis of improved pharmacological efficacy or safety.

There are many other examples of similar biological recognition of enantiomers which are related to natural or synthetic compounds in the field of agrochemicals or in the food and perfume industry.

The enantiomers of the pyrethroid, Cypermethrin, show different insecticidal activity.<sup>21</sup> The *S* enantiomer of the pesticide, fluazifop, is inactive, but is biochemically converted in soil (provided that it has not been sterilised) to the active *R* enantiomer.<sup>22</sup> The dextrorotatory enantiomers of the dialkylphosphates are pesticides in insects but the laevorotatory enantiomers are neurotoxic to humans.<sup>23</sup>

In the food, drink and perfume industries, taste or odour may be significantly different from one enantiomer to the other. Examples of terpenes where the difference is particularly striking are limonene, where the *R* enantiomer has an orange odour and the *S* enantiomer a lemon odour, and carvone, where the *R* enantiomer has a spearmint odour and the *S* enantiomer has that of caraway.<sup>24</sup> Chiral (*i.e.* enantioselective) analysis has been used in the industry to detect the adulteration of foodstuffs with cheap synthetic racemates of naturally occurring compounds.

There are many other fields where chiral analysis has proved useful, for instance in organic and inorganic synthesis, kinetics and geochronology (*i.e.* using the degree of amino acid racemisation to date organic material of archaeological importance).<sup>25</sup>

## **1.2                    TECHNIQUES AVAILABLE TO DISTINGUISH ENANTIOMERS**

### **1.2.1                Introduction**

This section refers to the *distinction* of enantiomers because it includes methods that are separatory and those that are non-separatory. Separatory methods may well be suitable for preparative applications, but the main thrust of this section is related to analytical applications.

Various techniques are available for enantiomeric distinction and these are reviewed in this chapter. Optical activity is discussed first because of its historical importance in the discovery of chemical chirality and because of its use as the only means of investigating this phenomenon over many years. After sections on NMR techniques and X-ray analysis there follows sections dealing with chromatographic techniques, this being most relevant to this research project, then electrochromatography and related capillary electrophoresis. Finally, a number of other techniques which have been used as a means to distinguish enantiomers are surveyed.

### 1.2.1.1 *Direct or Indirect Analysis*

Of the many techniques available for enantiomeric analysis, there are two general approaches, *direct* and *indirect* analysis. Direct analysis is the determination of the ratio of the enantiomers. Indirect analysis involves the derivatisation of the enantiomers with a homochiral reagent prior to the determination of the ratios of the resulting diastereoisomers. This ratio reflects the original ratio of the enantiomers. Many of the considerations for either approach are common to a number of analytical techniques. This is particularly true of the indirect approach, and therefore a section is included below on the subject, with further detail in the technique-specific sections later in this chapter.

### 1.2.1.2 *Advantages of the Use of Chiral Derivatisation Reagents (CDR)*

- a) CDRs can significantly lower detection limits (*e.g.* in liquid chromatography by incorporation of a chromophore or fluorophore).
- b) A CDR can be used highly selectively, in the presence of impurities which do not have the same functional group that is being utilised in the analyte. Derivatisation can increase the distinction between the analyte (as the derivative) and interferences (*e.g.* by increasing the retention time in chromatography or by incorporation of  $^{19}\text{F}$  in NMR).
- c) The reagent may have an appropriate probe that facilitates the analysis of the diastereoisomeric products (this is a highly technique-specific consideration and is discussed further in the relevant sections).
- d) The reagents are often inexpensive or may be easily prepared.
- e) In chromatography, the resulting derivatives can be analysed on relatively cheap achiral columns.

- f) It is normally possible to obtain the CDR in both enantiomeric forms (thus allowing the reversal of elution order in chromatography or the switching of diastereoisomer bands in NMR), which can be useful to position a minor diastereoisomer peak in a region where its resolution or quantification is improved.

#### 1.2.1.3 *Requirements of the Indirect Approach*

A successful chiral derivatisation reagent must fulfil the following requirements:

- a) It must be stable to racemisation under the conditions of the derivatisation process. Of course, the reaction conditions must be such that inversion does not occur in the analyte or the product either.
- b) The reaction to form diastereoisomeric derivatives must be quantitative so that kinetic resolution does not affect the results.
- c) Any purification step must not alter the relative proportions of the two diastereoisomers.
- d) Ideally, the reagent will have an appropriate probe that facilitates the analysis of the diastereoisomeric products. This consideration is very specific to the analytical technique being used.
- e) For maximum distinction of the diastereoisomers, it is normally preferred to have a short distance between the chiral centres of the reagent and analyte, or at least to allow the centres to approach each other closely.
- f) While it is normally stated that a CDR must be enantiomerically pure (or nearly so), this does not appear to be the case. Provided that the actual enantiomeric purity is known, it is always possible to apply a correction to obtain a valid

result. However, in practice, in order to avoid the possible effects of kinetic resolution, the reagent is usually added in excess. If there is a significant difference in the rate for the two stereochemical reactions, then the presence of enantiomeric impurity in the reagent becomes significant.<sup>26</sup>

- g) Although diastereoisomeric derivatives will normally have very similar detection properties (response ratios), it is possible that they will produce unequal responses at the detector, resulting in errors in quantification.<sup>27</sup>

## 1.2.2 Optical Activity

There have been many excellent reviews of optical activity, covering basic principles, optical rotation and circular dichroism, especially those of Mason,<sup>2, 28, 29</sup> Long and Urry,<sup>30</sup> Johnson,<sup>31</sup> and Abu-Shumays and Duffield.<sup>32</sup> Mason has also reviewed the historical development of an understanding of chirality, optical activity, and the origins of biomolecular chirality in nature.<sup>2, 28, 29, 33</sup>

### 1.2.2.1 *History and Principles of Optical Rotation and Circular Dichroism*

Optical activity was discovered by Biot around 1812.<sup>28</sup> He observed that quartz crystals rotated the plane of polarised light in some cases clockwise, in others, anti-clockwise. He distinguished two types of optical activity, one where the activity was a function of the crystal structure and was observed only in the ordered solid phase, the other where it was a property of the molecular structure, as in the case of natural camphor, since the activity was also present in the solution and the vapour phases.

In 1832 Herschel noted that the two types of quartz crystals existed as non-superimposable mirror images.<sup>28</sup> Investigating tartaric acid in wine in 1848, Biot's pupil, Pasteur, found that the same was true for the two crystalline salts of sodium ammonium tartrate, which he had separated manually. Further, he observed that the optical activity persisted in the solution

state. This led him to propose the concept of molecular dissymmetry, the absence of reflection symmetry, as distinct from the absence of any symmetry (asymmetry).<sup>28</sup> In those days of flatland molecular descriptions, this was difficult to accept. In 1873, having prepared more isomers of lactic acid than could be accommodated by two-dimensional molecular structures, Wislicenus proposed the need for a three-dimensional theory. The following year, van't Hoff and Le Bel provided the explanation on the basis of a tetrahedral model for tetravalent carbon. In 1895, Cotton discovered that optically active substances absorbed left- and right- circularly polarised light to different extents. The rotation of the plane of polarised light and the differential absorbance of left- and right- circularly polarised light, which peaks in the vicinity of an optically active absorption band, is commonly known as the Cotton Effect.<sup>28</sup>

#### 1.2.2.2 *Optical Rotation, Polarimetry and Circular Dichroism*

The amplitude-maxima of the oscillations of circularly polarised light rotate around the propagation axis and trace out a left-handed helix (left-circularly polarised light) or a right-handed helix (right-circularly polarised light).

Plane (linearly) polarised light can be regarded as the resultant of the contra-rotating fields of left- and right- circularly polarised light (Figure 1.1).

In passing through an optically active medium, one circularly polarised component may interact more strongly with the medium and thus be retarded *i.e.* it has a higher refractive index. On recombination of the two circularly polarised components, the resultant plane of linearly polarised light is therefore rotated relative to the incident plane.

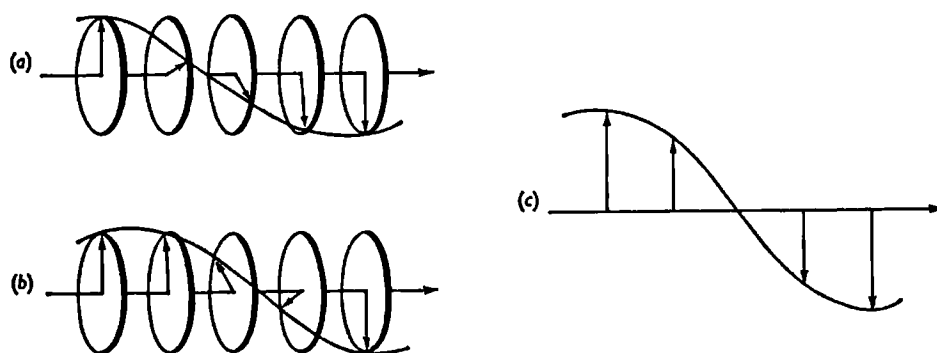
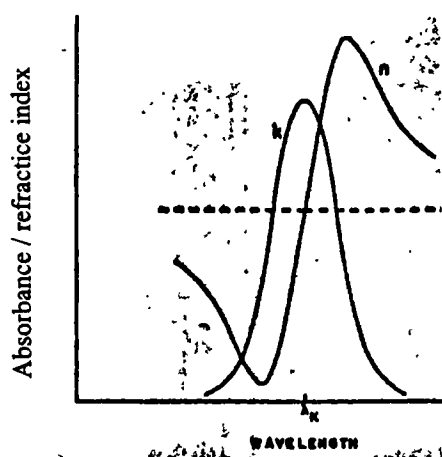


Figure 1.1 Representation of plane polarised light as the resultant of left- and right-circularly polarised light.

- a) Right-circularly polarised light   b) Left-circularly polarised light  
 c) Resultant of the combination of left and right-circularly polarised light *i.e.* plane - (linearly) polarised light

The rotation of the plane of the polarised light therefore arises from the difference in the interaction with the medium of the left- and right- circularly polarised light, *i.e.* the two hands of light have different refractive indices  $n_L$  and  $n_R$ . If  $n_L > n_R$  for a particular optically active compound, then  $n_L < n_R$  for its enantiomer.

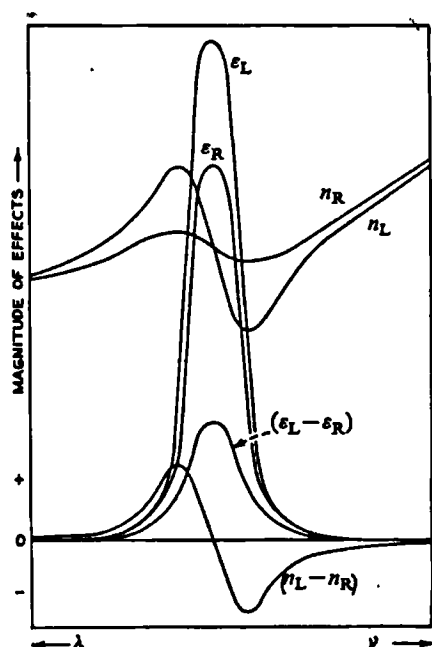


The refractive index of light in an optically *inactive* medium is wavelength dependent, with a minimum and maximum in the vicinity of an absorption band, as shown in Figure 1.2.

Figure 1.2 Dependence of absorbance and refractive index on wavelength in the region of absorbance due to a chromophore.

- k: absorbance  
 n: refractive index





Both the refractive index ( $\eta$ ) and the absorbance ( $\epsilon$ ) of each hand of light in an optically *active* medium will exhibit a similar wavelength dependence, as shown in Figure 1.3.

Figure 1.3 Absorption and refractive index spectra of left- and right-circularly polarised light in the absorbing region of a chiral compound.

The optical rotation, arising as it does from the difference in refractive indices, will therefore also be wavelength dependent, and will consist of a negative then a positive (Figure 1.4b), or, for the opposite enantiomeric medium, a positive then a negative response. This is known as the optical rotatory dispersion spectrum (ORD).

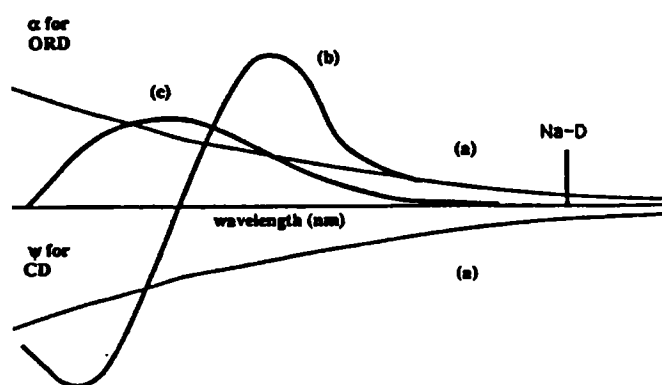


Figure 1.4 Optical rotatory dispersion and circular dichroism spectra.

- a) Plain ORD curve (in non-absorbing region)
- b) ORD curve in the region of UV absorbance due to chromophore influenced by a chiral environment
- c) Circular dichroism spectrum

Although generally less familiar, circular dichroism (CD), is more simple to describe. In passing through an optically active medium, the left- and right-circularly polarised light interact with the medium to different extents. Circular dichroism is the difference in the absorbance of left- and right-circularly polarised light, usually expressed as  $\Delta\epsilon = \epsilon_L - \epsilon_R$ . (Figure 1.3). As distinct from optical rotation, the *sign* of the circular dichroism for a particular transition, which may be positive or negative, is not wavelength-dependent.

Measurement of the rotation  $[\alpha]$  of the plane of polarised light has been the traditional means of determining enantiomeric purity and is used extensively in research and manufacturing, although it has limitations. Determination of optical rotation is normally measured at a single wavelength (polarimetry), usually 589 nm ( $[\alpha]_D$ ), while the electronic origin of the activity, the region of the Cotton effect, is usually at considerably lower wavelength (Figure 1.4b). Because the optical rotation is more spread over the spectral range, measured rotations can be misleading when attempting to predict absolute configuration, for instance using the octant or other rules, *e.g.* if a strong lower-wavelength optical activity swamps a weaker higher-wavelength (closer to 589 nm) band under consideration. Impurities in a sample can have profound effects on the measured rotation depending on the  $\lambda_{\max}$  of their dissymmetric chromophores.

CD has the advantage that it is more localised (with respect to wavelength) and can be used more selectively. The technique is therefore better suited to the assignment of absolute configuration and the determination of enantiomeric purity. One problem with CD is that the difference being measured,  $\Delta\epsilon$ , is typically 3-5 orders of magnitude smaller than the background ( $\epsilon$ ).

In the absence of impurities in a sample, the UV absorbance at a particular wavelength ( $A_\lambda$ ) gives a measure of the compound concentration, while the CD at a particular wavelength ( $\Delta A_\lambda$ ) gives a measure of the enantiomeric purity of the compound. In cases where the

concentration of sample is not known (*e.g.* in on-line spectrophotometric detectors for HPLC, or where small samples cannot be accurately weighed), the ratio of the CD to UV signals, typically determined at the  $\lambda_{\text{max}}$  of the CD, provide a convenient means by which the enantiomeric purity can be checked. This ratio ( $\Delta A_{\lambda} / A_{\lambda}$ ) is a measure of enantiomeric purity, independent of impurities (chiral or achiral), unless they absorb at that wavelength.

#### 1.2.2.3 *Problems Associated with Optical Activity Methods*<sup>34</sup>

If the maximum rotation of a compound is unknown, it must be determined, normally following a tedious resolution. Optical activity measurements are sensitive to solvent, concentration, temperature and pH (for instance if a chromophore like pyridine is altered by protonation). Rotations can be very low, which reduces the accuracy of measurement. Impurities, either chiral or achiral, will result in error in the determination of enantiomeric purity using optical activity methods.

#### 1.2.2.4 *Circular Dichroism in the Determination of Absolute Configuration*

While X-ray diffraction is the best tool for the determination of absolute configuration, the method is limited by the need for milligram quantities of reasonably pure crystalline material (section 1.2.4). If such a crystalline sample is not available, absolute configuration may be determined by CD, provided that the spectrum can be related to that of a compound of known absolute configuration. The only problem here is in deciding what compound can be used as a valid model. The model should have a similar chromophore to that of the compound under study, more specifically a similar chirophore. This makes the point that a compound with a similar chromophore is of no use if the chromophore is not affected by the asymmetry of the environment in the same way as the compound under study. A good guide to the validity of the model is the proximity of the  $\lambda_{\text{max}}$  and the magnitude of the molar CD at that wavelength,  $\Delta\epsilon_{\lambda}$ .

### 1.2.2.5 *Vibrational Spectroscopy*

Circular dichroism spectroscopy has mostly been used in the UV region, but has the potential to provide more structural information in the IR spectrum. Vibrational circular dichroism (VCD) has been successful, particularly using FTIR.<sup>35</sup>

However, there is an inherent drawback with IR. Optical activity is proportional to the frequency of the exciting light, which is several orders of magnitude smaller than the visible and near-UV frequencies. Fortunately, Raman scattering provides an answer, because the Raman effect gives complete vibrational spectra using visible excitation light. Thus, there is a difference in the intensity of scattered light depending on whether the incident light is left- or right- circularly polarised. This incident circularly polarised light Raman optical activity (ICP-ROA) provides spectra down to *ca.* 50 cm<sup>-1</sup>, where there is most stereochemical information, since skeletal deformation and torsional modes of vibration are important in this region.

An interesting variant that is currently being investigated is scattered circular polarisation Raman optical activity (SCP-ROA).<sup>36</sup> The incident light is linearly polarised and the difference in the scattered left- or right- circularly polarised light is measured. Incorporating spectral subtraction routines, this technique has been shown to provide useful chiroptical data even when chiral impurities are present.

## 1.2.3 **Nuclear Magnetic Resonance Spectroscopy**

### 1.2.3.1 *NMR Analysis Using Chiral Solvating Agents*

The related nuclei of two enantiomers have signals which are isochronous, *i.e.* they are chemical shift equivalent, because they are enantiotopic. However, when placed in a chiral environment, they become diastereoisotopic and therefore, in principle, anisochronous and may then be distinguished.

The simplest case of such an interaction with a chiral solvating agent (CSA) is where a homochiral CSA ( $C_R$  or  $C_S$ ) interacts with each of the solute enantiomers ( $X_R$  and  $X_S$ ) to form binary association complexes  $X_R C_R$  and  $X_S C_R$ . Equations for the equilibria are therefore:



Under normal conditions, where exchange is rapid, each solute enantiomer will be observed as the weighted average of two signals.  $X_R$  will appear at chemical shift  $\delta_{OBS}$ , being the weighted average of the shifts for the complexed and uncomplexed solutes,  $\delta_{X_R}$  and  $\delta_{X_R C_R}$  respectively. Similarly,  $X_S$  will appear at chemical shift  $\delta'_{OBS}$ , being the weighted average of the shifts  $\delta_{X_S}$  and  $\delta_{X_S C_R}$ . At equilibrium, the uncomplexed solutes,  $X_R$  and  $X_S$  have fractional populations ( $p$  and  $p'$ ) so that:

$$\delta_{OBS} = p\delta_{X_R} + (1 - p)\delta_{X_R C_R} \quad \text{and} \quad \delta'_{OBS} = p'\delta_{X_S} + (1 - p')\delta_{X_S C_R}$$

The observed anisochrony  $\Delta\delta$  is therefore:  $\Delta\delta = |\delta_{OBS} - \delta'_{OBS}|$

The observed anisochrony clearly depends on two factors. One is the intrinsic anisochrony between the diastereoisomeric complexes  $X_R C_R$  and  $X_S C_R$ , the other is the difference between the fractional populations of the association complexes. Much work has been done to maximise these terms, pioneered by Pirkle<sup>37</sup> in 1966. The technique has been well reviewed by Weismann.<sup>38</sup>

Assuming that adequate anisochrony has been obtained, two signals will be observed, and their relative intensities (integrals) will be proportional to the relative proportions of the solute enantiomers, allowing rapid direct determination of enantiomeric purity.

It is important to note that the CSA does not have to be enantiomerically pure (or even known), but as it tends to a racemic mixture,  $\Delta\delta$  tends to zero.

### 1.2.3.2 *NMR Analysis Using Chiral Shift Reagents*

The principles of the behaviour of chiral shift reagents (CSRs) are in many ways similar to those of CSAs and have been reviewed by Fraser.<sup>39</sup> A typical shift reagent is a lanthanide metal complex which is a Lewis-acid and capable of forming addition complexes with an organic base. This induces a downfield shift,  $\Delta\delta$ , which increases with the addition of more shift reagent, up to a maximum value. The magnitude of  $\Delta\delta$  is related to the proximity of the reagent to the signal being observed.

The first use of a CSR was described by Whitesides and Lewis<sup>40</sup> who prepared the chiral ligand 3-pivaloyl-*d*-camphor (pvc) and its europium complex, Eu(pvc)<sub>3</sub>. They were able to resolve the proton resonances of the enantiomers of 1-phenylethylamine and 1-phenylethanol.

### 1.2.3.3 *NMR Analysis Using Chiral Derivatisation Reagents*

Chiral derivatisation is used in NMR to convert enantiomers to diastereoisomers so that enantiotopic signals become diastereotopic. Analysis of the diastereotopic signals provides a measure of the original enantiomer ratio. In some cases the difference in the chemical shift of the diastereotopic signals ( $\Delta\delta$ ) gives an indication of the relative stereochemistry of each diastereoisomer and, because the absolute stereochemistry of the derivatisation reagent is known, the absolute stereochemistry of the original enantiomer can be deduced.

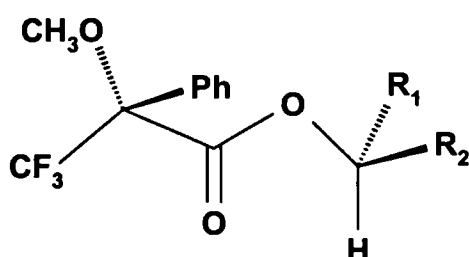
The general advantages and limitations of CDRs are discussed in sections 1.2.1.2-3.

A special consideration that applies to NMR is that derivatisation can be used to incorporate an appropriate probe (*e.g.* a silyl methyl, methyl, methoxy, or *tert*-butoxy group) that affords clearly resolved NMR signals. A well-defined conformational preference that places diastereotopic groups in distinctly different magnetically anisotropic environments will maximise both  $\Delta\delta$  and the ease of establishing the absolute

configuration of the analyte enantiomer. Alternatively, a new nucleus (*e.g.*  $^{19}\text{F}$ fluorine,<sup>41</sup>  $^{28}\text{Si}$ silicon<sup>42, 43</sup>) can be added which will further enhance the selectivity.

A reagent that fulfils all of the above requirements and is therefore the best known in this context is Mosher's reagent,  $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid (MTPA)<sup>41</sup> (Figure 1.5). A wide variety of carbinols, amines and amino-alcohols react with MTPA chloride to form the corresponding esters and amides.

In the preferred conformation of the Mosher's ester, the  $\text{CF}_3$  and the carbonyl groups and



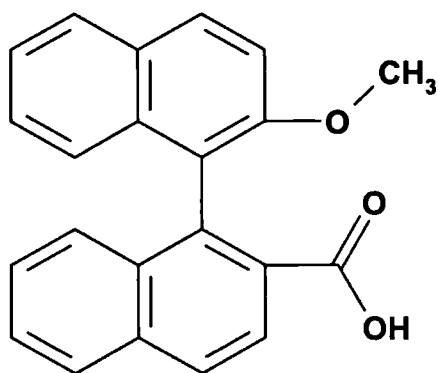
the carbonyl hydrogen lie approximately in the same plane.  $\text{R}_2$  is shielded by the phenyl group and will appear upfield (lower  $\delta$ ) relative to the MTPA ester derived from the other enantiomer of the alcohol.

Figure 1.5 The preferred conformation of a Mosher's acid derivative

A further advantage of this reagent is that it can be used, with high selectivity, in  $^{19}\text{F}$  NMR.

In cases where  $\Delta\delta$  is insufficient, or bands overlap, an obvious solution is to use a spectrometer with increased resolution. If this is not possible, then the addition of an achiral lanthanide shift reagent can induce a larger inequivalence.<sup>44</sup>

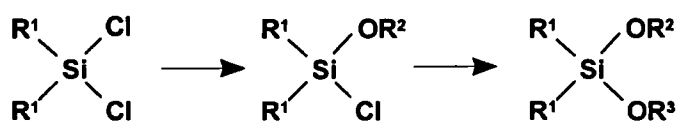
Among the many other CDRs that have been reported a few are more relevant to the research presented here, being based on  $\text{C}_2$ -symmetry. One recent example is that of axially chiral 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid (MBNC)<sup>45</sup> (Figure 1.6).



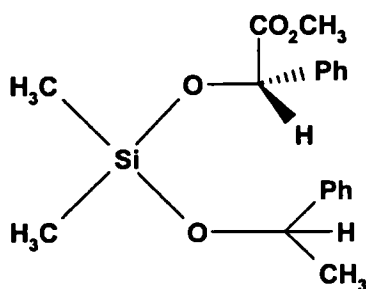
The MBNC derivatives of (-)-menthol were prepared and  $\Delta\delta_{\text{H}}$  determined for each proton in the menthyl group. Values of  $\Delta\delta_{\text{H}}$  as large as 0.47 were observed, and chemical shifts as low as -0.23 were obtained.

Figure 1.6 MBNC used to prepare esters for NMR studies.

Another recent example that is relevant to the work presented here involves silicon.<sup>42</sup> Chan *et al* prepared diastereoisomeric acetals by incorporating two chiral alcohols, one homochiral ( $\text{R}^2\text{OH}$ ) and one of unknown enantiomeric purity ( $\text{R}^3\text{OH}$ ), with a dichlorosilane as shown in Figure 1.7.



In the example in the scheme, *S*-(+)-methyl mandelate was used to distinguish the enantiomers of 1-phenylethanol.



The  $\text{SiCH}_3$  groups in the diastereoisomeric products had  $\Delta\delta = 0.095$  ppm.

Figure 1.7 Diastereoisomeric chiral silyl acetals prepared by Chan<sup>42</sup> for NMR studies.

Many other CDRs have been developed to extend the range of compounds which can be derivatised or to improve the factors listed above. The topic has been reviewed by Yamaguchi<sup>46</sup> and Parker.<sup>47</sup>



#### 1.2.4 X-Ray Diffraction

It was only in 1951 that Bijvoet was able to confirm, using the anomalous diffraction of X-rays, that the absolute configuration of (+)-tartaric acid was correctly represented by the conventional structure proposed by Fischer 60 years earlier.<sup>2</sup> This also assured the absolute configuration of compounds which had previously been related to (+)-tartaric acid *via* chemical interconversions.

Subsequently, X-ray diffraction has been used directly in the routine determination of the absolute configuration of other compounds, including transition metal complexes. Ordinary X-ray analysis gives information on the *relative* spatial distribution of atoms, and can therefore discriminate between diastereoisomers. Anomalous X-ray scattering (Bijvoet X-ray analysis) is necessary to provide *absolute* configuration information.<sup>48,49</sup> The method is limited by the need for milligram quantities of reasonably pure crystalline material. If such a crystalline sample is not available absolute configuration may be determined by CD, provided that the spectrum can be related to that of a compound of known absolute configuration (section 1.2.2.4).

#### 1.2.5 Gas Chromatography

##### 1.2.5.1 *Separation of Enantiomers by GC with a Chiral Stationary Phase*

The first enantiomer resolution with a chiral (*i.e.* homochiral) GC stationary phase was achieved by Gil-Av *et al*<sup>50</sup> in 1966, using glass capillaries coated with N-trifluoroacetyl-L-isoleucine lauryl ester. There have been many developments since, with recent reviews by Schleimer *et al*<sup>51</sup> and Schurig.<sup>52</sup>

A chiral (*i.e.* homochiral) stationary phase works on the basis that one enantiomer is retained preferentially with respect to the other. This is normally considered in terms of a three-point interaction between the stationary phase and the analyte. The concept is the

same as that proposed in 1933 by Easson and Stedman<sup>53</sup> to describe the interaction of racemic drugs with receptors and enzyme-substrate interactions. The three-point interaction was applied to paper chromatography by Dalglish<sup>54</sup> in 1952. Similar considerations are valid in GC chiral separations. Figure 1.8 shows one particular relative orientation of the stationary phase and the analyte.

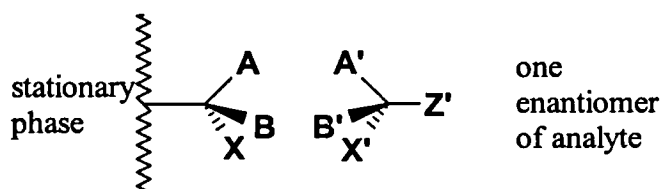
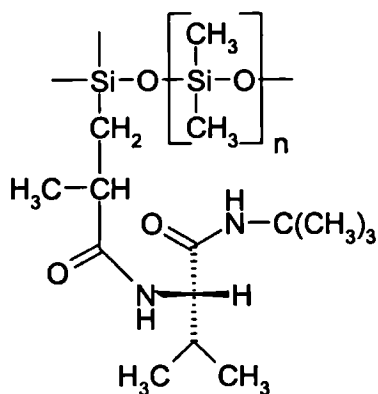


Figure 1.8 The three-point interaction model to illustrate stereoselective retention in chromatography.

If the interactions A-A', B-B' and X-X' are the strongest attractive interaction combination, then this enantiomer will be more strongly retained on the stationary phase than its antipode, which cannot achieve the same combination of attractions.

The advent of fused-silica capillary columns has led to an upsurge in the number of chiral GC phases being investigated, and a range of chiral GC columns is now commercially available. Schurig has classified chiral GC phases into three types, according to their mode of retention.



Chirasil-Val

The first class of chiral GC phases is based on chiral amino acid derivatives, where hydrogen bonding is the predominant mechanism of interaction with analytes. The most familiar phase in the class is Chirasil-Val, which is available in both enantiomeric forms, and can separate all proteinogenic amino acids (achirally derivatised) in less than 25 minutes.

The second class of chiral GC phase was introduced by Schurig in 1977<sup>55</sup> and was originally based on the chiral metal co-ordination compound carbonylrhodium(I)-3-trifluoroacetyl-(1*R*)-camphorate. Unlike the hydrogen-bonding phases, the metal co-ordination phases do not require that analytes need achiral derivatisation (*e.g.* Figure 1.9).

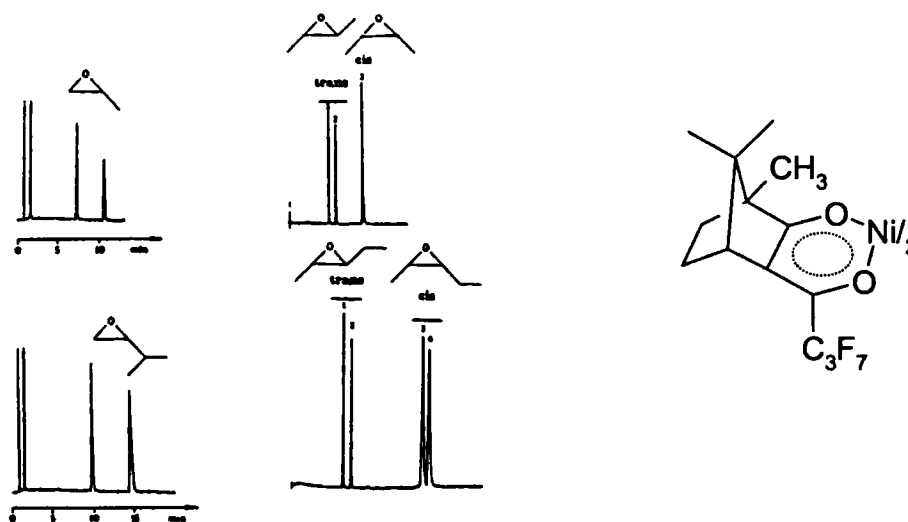
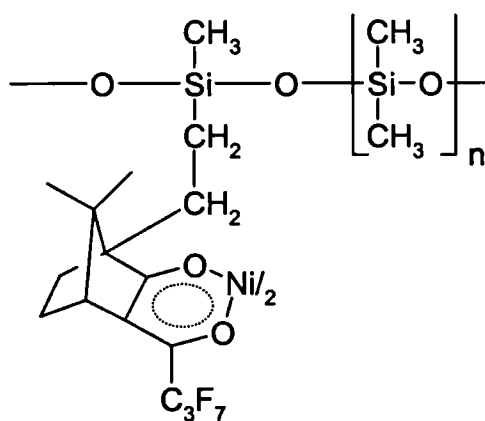


Figure 1.9 Separation of chiral epoxides on nickel(II)bis[3-heptafluorobutanoyl]-(1*S*)-10-ethylidenecamphorate] (0.125 molal in OV-101) between 70 and 90°C.<sup>56</sup>



The above phases have proved very versatile and have resolved a wide variety of compounds. They are, however, of low thermal stability (to 120°C), but this has now been improved by the preparation of immobilised polymeric CSPs such as Chiralsil-Metal shown left.

The third class of chiral GC phase uses inclusion complexation of analytes in cyclodextrin or its derivatives. The first such phases were developed in 1983<sup>57</sup> and used  $\alpha$ -cyclodextrin coated on packed columns. Many developments have occurred since and a variety of polysiloxane bonded phases are now commercially available.

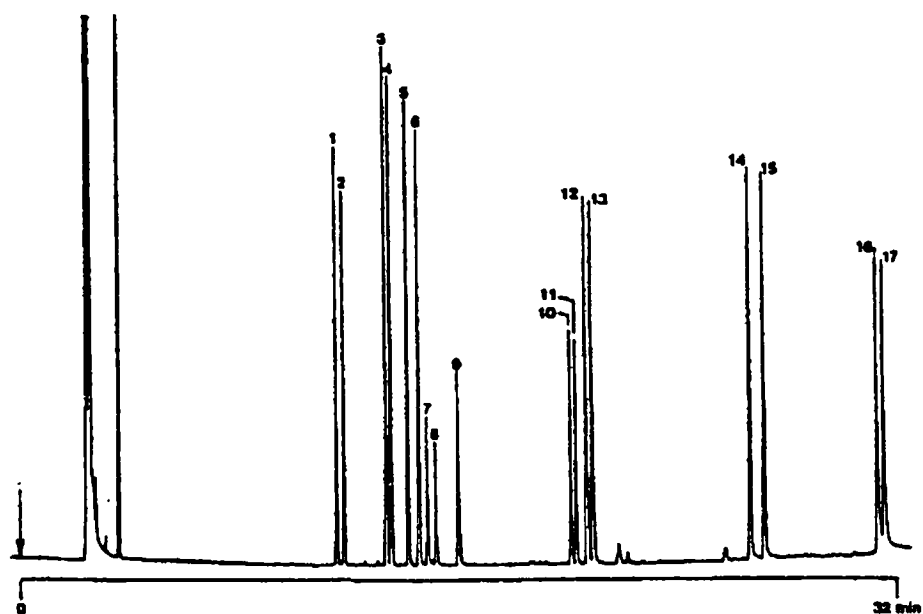


Figure 1.10 Enantiomer separation on modified cyclodextrin phase:

$\alpha$ -pinene (1, 2), *trans*-pinane (3, 4), *cis*-pinane (5, 6), 2,3 butanediol (*rac*) (7, 8), 2,3 butanediol (*meso*) (9),  $\gamma$ -valerolactone (10, 11), 1-phenylethylamine (12, 13), 1-phenylethanol (14, 15), and 2-ethylhexanoic acid (16, 17) by GC on heptakis(2,3,6-tri-O-methyl)- $\beta$ -cyclodextrin (10% w/w in OV-1701) at 50°C, 50 m x 0.25 mm ID fused-silica column, film thickness 0.25  $\mu\text{m}$ .<sup>58</sup>

Figure 1.10 shows the separation of the enantiomers of a wide range of compounds present in the 'Schurig test mixture'. This chiral test mixture was devised to probe the efficiency, enantioselectivity and inertness of permethyl- $\beta$ -cyclodextrin-OV-1701 columns. In 1994<sup>52</sup>, Schurig stated that 'the rationalisation of chiral recognition involving cyclodextrin derivatives is difficult as almost all classes of chiral compounds are susceptible to enantiomer separation on a certain cyclodextrin-derived CSP, often with no logical dependence on molecular shape, size and functionalities. Obviously, multimodal recognition processes take place, which may involve *inter alia* inclusion, hydrogen bonding, dipole-dipole interaction and other forces. As enantiomer separations have also been observed with amylose derivatives, inclusion is not a prerequisite for chiral recognition using carbohydrates'.

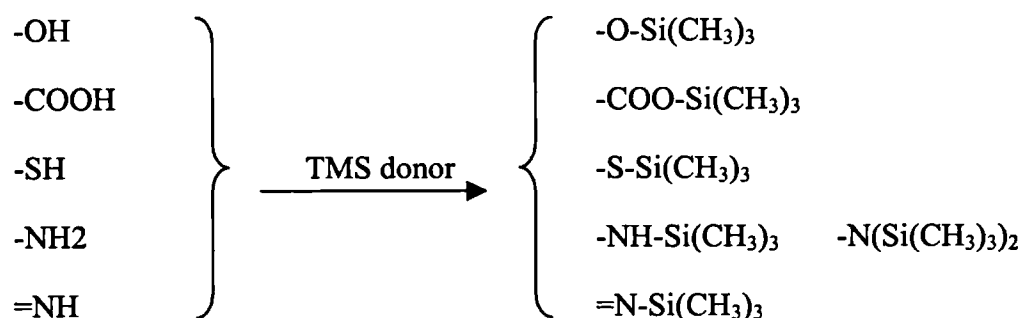
### 1.2.5.2 Chiral Derivatisation for Gas Chromatography

The general advantages and limitations of CDRs are discussed in sections 1.2.1.2-3.

Derivatisation techniques and their pros and cons have been reviewed with respect to gas chromatography, both achiral<sup>59, 60</sup> and chiral.<sup>60, 61, 62, 63, 64</sup> Reviews by Gal<sup>65</sup> and Skidmore<sup>61</sup> discuss general derivatisation reactions for chromatography according to the functional group of the analyte and lists various reagents.

A special consideration that applies to GC is that derivatisation of analytes can be used to reduce polarity and the tendency to form hydrogen bonds which thereby increases volatility, reduces thermal decomposition and peak tailing.<sup>59, 66</sup>

Of particular interest in this research is the formation of silyl ethers, commonly used in GC to improve volatility and a variety of reagents are available.<sup>60, 67, 68</sup> The most commonly formed are trimethylsilyl (TMS) derivatives, from the reaction of a TMS donor *e.g.* chlorotrimethylsilylane to replace an active hydrogen atom of the analyte as shown in Scheme 1.1.



Scheme 1.1 Examples of TMS derivatives typically formed prior to GC analysis.<sup>68</sup>

Derivatisation prior to GC has also often been used to improve sensitivity, for instance by incorporating nitrogen or halogen-substituted groups for selective detection by nitrogen detectors or electron capture detectors respectively. This has been useful in achiral<sup>69, 70</sup> and

chiral<sup>64</sup> analysis. Derivatisation can also be used to impart sensitivity/selectivity for mass spectrometric detection.<sup>70, 71, 72,</sup>

There has been little research reported on the preparation of chiral silyl ether derivatives (Feibush and Spialter,<sup>73</sup> Kaye and Learmonth,<sup>43</sup> Brooks *et al*<sup>74</sup>). Feibush carried out an early study into the GC separation of simple symmetrically substituted dichiral ethers, alkoxysiloxanes and disiloxanes. Separation of the diastereoisomeric ethers was best ( $\alpha = 1.09$ ), the alkoxysiloxanes next ( $\alpha = 1.02$ ), while the disiloxanes were unresolved.

Kaye prepared diastereoisomeric silyl acetals from menthol or borneol and chiral secondary alcohols. However, the GC separations were poor ( $\alpha \leq 1.005$ ,  $R_s \leq 0.88$ ) and would be inadequate for analytical work.

Brooks *et al* prepared diastereoisomeric silyl ether derivatives from racemic *tert*-butylmethoxyphenylsilyl bromide, achieving baseline resolution by GC for the diastereoisomers of selected compounds. Limitations noted for this approach were the unavailability of homochiral reagent, its stability with respect to inversion, and the potential for the derivatisation reaction to proceed with a mixture of inversion and retention of configuration at the silicon atom.

## 1.2.6 Liquid Chromatography

### 1.2.6.1 Separation of Enantiomers by HPLC with a Chiral Stationary Phase

The concept of a three-point interaction between the stationary phase and the analyte was discussed in Section 1.2.5.1 and depicted in Figure 1.8.

Various chiral stationary phases (CSPs) have been used since the turn of the century in attempts to effect enantiomeric resolution. In 1904, Wilstätter proposed the use of wool to

resolve racemic dyes, but this was not realised until 1922, when Ingersoll and Adams obtained enantioselective batch adsorption of a racemic aniline dye on wool.<sup>75</sup>

The first true chromatographic separation was achieved in 1938 by Henderson and Rule<sup>76</sup> who partially separated racemic camphor derivatives on a column filled with lactose.

An interesting development in the resolution of the enantiomers of amino acids arose from an accidental discovery in 1951 by Kotake *et al.*<sup>77</sup> They succeeded in separating enantiomers from certain racemic amino acids by paper chromatography using a homochiral eluent. However, on repeating the work using the opposite enantiomer of the eluent the anticipated inversion of elution order was not obtained. Further, the same separation occurred when racemic and achiral solvents were used, leading to the conclusion that the resolution was due to the chirality of the cellulose stationary phase.

Various potential chiral stationary phases have been investigated, including other convenient naturally occurring materials such as quartz, powdered silk and potato starch<sup>78, 79, 80</sup> as well as modified natural and synthetic phases.

The use of CSPs has probably become the most widely used technique for enantiomeric analysis, having blossomed since the first commercially available columns were packed with material developed by Pirkle.<sup>81</sup> Many review papers, including those by Pirkle,<sup>80</sup> Taylor<sup>82</sup> and complete volumes, edited by Lough,<sup>83</sup> Krstulovic,<sup>84</sup> and Subramanian,<sup>85</sup> have been devoted to liquid chromatographic separations, mostly concerned with CSPs.

In the last 15 years the number of commercially available CSP columns has increased to over 150<sup>86</sup> and, in making a greater choice available, made it difficult for the chromatographer to select the appropriate column. Simultaneously, there has been some progress in the understanding of the "recognition processes" involved in the distinction of enantiomers, notably by Pirkle, and by others specialising in other types of CSPs. Also,

there has been a limited advance in the understanding of enantioselective binding in chromatography by molecular modelling. Much of this work has been done by Lipkowitz, who ended his review written in 1991<sup>87</sup> with the comment that "we have a long way to go ... molecular simulation is only in its infancy".

There has been a natural evolution of CSPs from a number of different starting points. Similar phases exhibit similar interactions with solutes, so it has been useful to class CSPs based on how they work. This was done by Armstrong<sup>25</sup> and by Meyer *et al*<sup>88</sup> and subsequently by Wainer,<sup>89</sup> the latter being the generally accepted classification. Wainer's approach was to split the chromatographic process into two main steps. Firstly, a solute-CSP diastereoisomeric complex is formed. Secondly, the difference between the diastereoisomeric complexes results in different chromatographic behaviour. The first step is more readily adaptable to a classification system, which groups CSPs into five types:

**I.** Where the solute-CSP complexes are formed by attractive interactions, hydrogen bonding,  $\pi$ - $\pi$  interactions, dipole stacking, *etc.* between the solute and CSP. Having been introduced by Pirkle, these are often referred to as 'Pirkle phases', and have been recently reviewed by Welch,<sup>90</sup> Doyle<sup>91</sup> and Macaudiere *et al*.<sup>92</sup>

**II.** Where the primary mechanism for the formation of the solute-CSP complex is through attractive interactions, but where inclusion complexes also play an important role. This class of CSPs includes the derivatised polysaccharides, particularly cellulose and amylose, which have been the most useful of all the types of CSP. They were recently reviewed by Okamoto and Kaida<sup>93</sup> and, with many examples, by Okamoto.<sup>94</sup>

**III.** Where the solute enters into chiral cavities within the CSP to form inclusion complexes.

The most important phases in this class are the cyclodextrins, reviewed by Han and



Armstrong,<sup>95</sup> the group of helical polymers, reviewed with many examples by Okamoto,<sup>96</sup> and microcrystalline cellulose triacetate reviewed by Okamoto.<sup>97</sup> C<sub>2</sub>-symmetric chiral chromatographic separation were discussed by Tichý *et al.*,<sup>98</sup> containing many interesting references to similar phases.

**IV.** Where the solute is part of a diastereoisomeric metal complex (chiral ligand exchange chromatography).

This class of CSP was reviewed by Davankov.<sup>99</sup>

**V.** Where the CSP is a protein and the solute-CSP complexes are based upon combinations of hydrophobic and polar interactions. The protein phases behave rather differently from the type 1 phases. Enantiomeric selectivity can be very high, but as the chromatographic kinetics are slower, chromatographic efficiency is normally lower. Because of the difficulty of modelling the protein and the relevant stereoselective interactions in the chromatographic process, it is normally more difficult to predict whether a protein phase will effect a given separation. Separations using this class of CSP were recently reviewed by Allenmark and Anderson<sup>100</sup> and also by Wainer.<sup>101</sup>

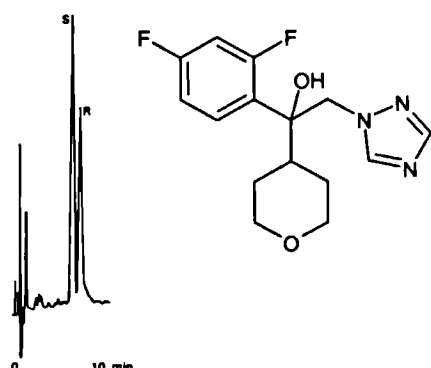
Finally, although this type of phase was not mentioned in Wainer's classification, there is an interesting variant, molecular imprinted stationary phases, which falls into the type III class. This type of phase is one of the earliest synthetic CSPs, having been used as early as 1952, and is prepared by polymerising a functionalised monomer around homochiral template molecules, which are subsequently extracted leaving chiral sites having the potential to discriminate between enantiomers (particularly of the template compound). This technique, which has not proved very successful and has therefore not been commercialised, was reviewed by Sellergren<sup>102</sup> and Kempe and Mosbach.<sup>103</sup>

### 1.2.6.2 Separation of Enantiomers by HPLC with a Chiral Mobile Phase

The use of chiral mobile phases (CMPs) has been the less-favoured form of direct chromatographic separation. The major advantage of CMPs is that ordinary cheap achiral columns can be used, and small amounts of homochiral CMP additives prepared or bought to test a separation. Pirkle and Sikkenga<sup>104</sup> used as a CMP additive a homochiral fluoroalcohol (that which had proved successful in NMR CSA studies) to partially resolve a racemic sulfoxide on a silica column, with CCl<sub>4</sub> as solvent. They later found that the fluoroalcohol performed better for this separation when used as a CSP agent.

CMP separations have been reviewed by Lam,<sup>105</sup> Szepesi,<sup>106</sup> Pirkle,<sup>107</sup> Clark,<sup>108</sup> and Pettersson.<sup>109</sup> Ligand exchange chromatography (mentioned in section 1.2.6.1 with regard to CSP applications) can also be performed with homochiral ligands in the mobile phase. Other forms of ion-association agents have been investigated, as have non-metallic complexation agents, particularly cyclodextrins and their derivatives.

In CMP resolutions three separation processes may occur simultaneously, which will often work against each other. Firstly, there may be a difference in the degree of complexation of the analyte enantiomers with the homochiral ligand. Secondly, the diastereoisomeric complexes may be differentially retained on the stationary phase. Thirdly, the homochiral ligand may be adsorbed on the stationary phase, and the analyte enantiomers experience differential adsorption on a now-chiral stationary phase.



Nevertheless, many CMP separations have been reported in the literature. The enantiomers of the antifungal agent shown here were resolved using 40mM  $\beta$ -cyclodextrin dissolved in the mobile phase, with a C<sub>18</sub>-bonded stationary phase.<sup>110</sup>

Whereas, as previously discussed in relation to separation on chiral stationary phases, a three-point interaction between the chiral stationary phase and the analyte enantiomer is necessary to achieve enantioselectivity, the situation may be different in separations with chiral mobile phases. Davankov<sup>111</sup> pointed out that a two-point interaction is sufficient for chiral recognition, provided that the two components of the diastereoisomeric adduct simultaneously interact with a sorbent surface. Thus the locating effect of the stationary phase reduces the need for three-point interaction between the analyte enantiomer and the chiral component of the mobile phase, so that a two-point interaction between them is sufficient for chiral separation.

#### *1.2.6.3 Separation of Enantiomers Following Chiral Derivatisation*

The general advantages and limitations of CDRs are discussed in sections 1.2.1.2-3.

A review by Gal<sup>65</sup> discusses general derivatisation reactions for chromatography according to the functional group of the analyte and lists various reagents. Reviews by Pirkle,<sup>112</sup> Lindner and Pettersson,<sup>113</sup> Ahnoff and Einarsson<sup>114</sup> and Görög and Gazdag,<sup>115</sup> are of particular relevance to liquid chromatography. The latter two reviews include tables of derivatisation reactions according to the functional group of the analyte, while the previous paper includes a table of homochiral reagents.

A special consideration that applies to HPLC is that derivatisation can be used to add a chromophore to decrease the limit of detection by spectrophotometry and to extend the range of detectors that can be used. A table in the above-mentioned review<sup>116</sup> gives many examples of CDRs providing a UV chromophore or fluorophore and also notes the type of HPLC (normal- or reversed-phase) used for the separation.

As with GC, cost can be an important factor in deciding to use chiral derivatisation in preference to direct chiral separation because of the higher cost of chiral stationary phases

and of homochiral additives for the chiral mobile phase approach. A further advantage is that chromatographic efficiency is normally higher on achiral than on chiral stationary phases, allowing more accurate analysis, as a result of improved signal/noise ratio and resolution of stereoisomers. CDRs for preparative chromatography may be a practical proposition provided that the required enantiomers can be recovered from the resolved diastereoisomers.

The assignment of absolute configuration on the basis of elution order may be possible, provided that similar compounds have been studied. It is important to know the absolute configuration of the CDR and the chromatographic retention mechanism if the absolute configuration is to be assigned with confidence.<sup>117</sup>

### **1.2.7 Electrochromatography**

This technique uses capillary electrophoretic equipment and, although essentially a chromatographic method, it has been considered as a branch of capillary electrophoresis,<sup>118</sup> and is discussed in section 1.2.11.1.

### **1.2.8 Supercritical Fluid Chromatography**

Supercritical fluid chromatography (SFC) has been defined as a chromatographic technique in which the mobile phase is at pressures and temperatures above or just above the critical point and was recently reviewed by Petersson and Markides.<sup>119</sup> By adjusting the temperature and pressure, the supercritical fluid can become more gas- or liquid-like and the chromatography therefore can be made to be more similar to GC or HPLC.

SFC often gives better results than either GC or HPLC for a number of reasons. Carbon dioxide is normally used as the mobile phase in SFC and provides greater solvating power than is available in GC. Lower temperatures are used in SFC than in GC, which results in greater enantiomeric selectivity and reduces the potential for racemisation or thermal

degradation of analyte or chiral stationary phase. However, mass transfer is faster in GC, leading to higher chromatographic efficiency, and this can result in better resolution by GC. Mass transfer is faster in SFC than in HPLC, but selectivity is normally greater in HPLC. Accordingly, SFC often provides higher resolution. Some references to comparisons of the various chromatographic techniques are given in Section 1.2.10.

### 1.2.9 Thin-Layer Chromatography

This technique is obviously related to column liquid chromatography and has the advantages and disadvantages discussed with reference to achiral<sup>120</sup> and chiral<sup>121, 122</sup> separations.

Essentially, the disadvantages of low chromatographic efficiency, difficulty of detection and lower accuracy of quantification can be overshadowed by the low cost of the plates, and the ability to run many samples simultaneously.

All liquid chromatographic modes may be used, including CSP (*e.g.* Pirkle-type and ligand-exchange phases) and CMP (*e.g.* cyclodextrins).

### 1.2.10 Selection of Chromatographic Technique

The decision as to which chromatographic techniques to consider for an enantiomer separation is usually one based on the nature of the analyte, the purpose of the analysis, the availability of columns and equipment, economy, the nature of the required analysis, and will be made with the guidance of literature reports of separations of similar compounds. Two specialised aids to the decision-making process are available. One is a survey<sup>123</sup> of all chiral chromatographic separations, including indexes of analytes, chiral stationary phases, chiral mobile phases, derivatisation techniques and authors. The other is a literature database, known as *Chirbase*, developed by Roussel *et al.*<sup>86</sup> Chromatographic information (including the enantiomeric selectivity,  $\alpha$ , and the resolution,  $R_s$ ) together with

bibliographic details has been abstracted from the literature for most reported chiral separations achieved using a chiral stationary phase (whether by liquid, supercritical fluid or gas chromatography). Being a graphical molecular database, it can still provide help for column selection for a novel analyte, using substructure searching to locate methods which have been successful for similar analytes.

There have been a number of papers comparing chromatographic techniques for chiral resolution. Lynam and Nicolas,<sup>124</sup> and Röder, Pirkle *et al*<sup>125</sup> compared SFC with HPLC, and Petersson and Markides<sup>119</sup> compared SFC with GC and HPLC.

Capillary electrochromatography (CEC) has been compared with capillary electrophoresis (CE) by Li and Lloyd.<sup>126</sup> EC has been compared with HPLC, GC and SFC by Schurig,<sup>127</sup> an excellent chromatographic comparison using the same capillary column. In this case, EC provided the optimum chromatographic performance.

Overall, it is not possible to state that one technique is consistently better for all enantiomer separations.

#### **1.2.11 Electrophoretic Techniques**

Capillary electrophoresis (CE) covers a range of techniques: isotachopheresis (ITP), isoelectric focusing (IEF), capillary gel electrophoresis (CGE), capillary zone electrophoresis (CZE), electrokinetic chromatography (EKC), and electrochromatography (EC). The distinction between these techniques is not always clear.<sup>128</sup> Enantiomer separation by CE techniques has been reviewed recently.<sup>128, 129, 130, 131</sup>

The techniques which have been used most for enantiomer separation are CZE and EKC. CZE separations use additives which are similar to those used in CMP applications in HPLC. Chiral separation has been achieved by chiral ligand exchange compounds, crown

ethers, oligosaccharides or, more commonly by one of a wide range of cyclodextrin derivatives.

Analytes which are not charged or are non-ionic migrate with the same velocity (that of the electroosmotic flow) and therefore cannot be separated by CZE. This can be overcome by adding a charged component to the aqueous phase which acts as a pseudo-stationary phase. This mode is known as electrokinetic chromatography and if the charged component forms micelles it is termed micellar electrokinetic chromatography (MEKC).

Examples of compounds used as pseudo-stationary phases include ionic micelles, bile salts (*e.g.* Figure 1.11) cyclodextrin derivatives having ionic groups, microemulsions and proteins. An example of a separation using bile salt is shown in Figure 1.12.

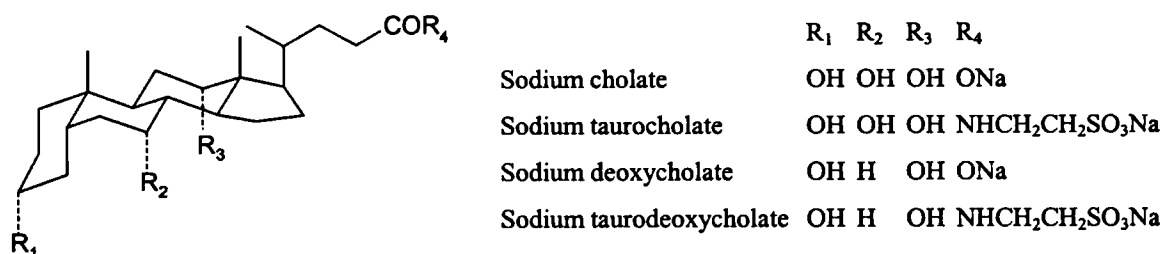


Figure 1.11 Structures of some bile salts used in MEKC.<sup>132</sup>

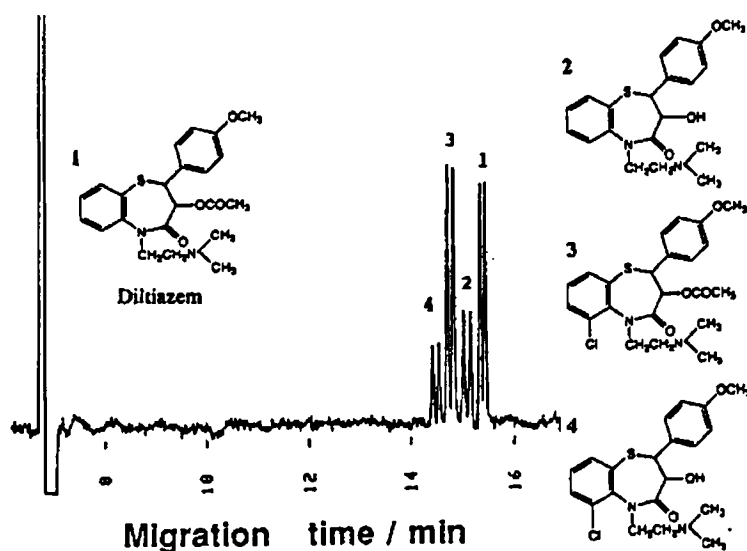


Figure 1.12 Separation of enantiomers of diltiazem and related compounds by MEKC with bile salt.<sup>133</sup>

Although electrochromatography has been considered as a branch of CE,<sup>118</sup> the separation principle is that of conventional liquid chromatography, only differing in that the driving force for the mobile phase is provided by electroosmotic flow rather than by hydraulic pressure from a mechanical pump.

### **1.2.12 Other Chiral Analytical Techniques**

#### **1.2.12.1 *Kinetic Resolution and other Chemical Methods***

Kinetic resolution was reviewed by Mislow<sup>134</sup> and by Raban and Mislow.<sup>135</sup> Kinetic resolution, *i.e.* where two enantiomers react with a chiral reagent at different rates, is the essential feature of the 'double resolution' method of Horeau, the principle of which can be illustrated as follows. If a racemic sample of the analyte is reacted with an insufficient quantity of homochiral reagent, the remaining analyte will be enriched in one enantiomer. This is measured, typically by optical rotation, to give a value which reflects that enrichment (but cannot be used directly because the absolute rotation of the analyte is obviously not known). An equation can be written which includes two unknowns, the absolute rotation of the analyte and the fraction of the homochiral reagent that reacted with one enantiomer of the analyte. The experiment is repeated, but this time using a racemic sample of the reagent and a deficiency of the actual analytical sample. Now there will be an excess of reagent, the enantiomeric enrichment of which is again measured by the same technique. A similar equation can be written which includes the same two unknowns. Simultaneous solution of these equations provides a value for the absolute rotation of the analytical sample and hence its enantiomeric purity.

A chemical method for the determination of absolute configuration was discussed by Mislow.<sup>134</sup> A compound of unknown configuration may be chemically converted to a compound for which the absolute configuration is known. Provided that the conversion



proceeds with stereochemical integrity, *i.e.* so that no bonds adjacent to the asymmetric centre are broken or made, the configuration of the product will remain identical with that of the original compound. A technique such as polarimetry is then used to determine the absolute configuration of the product and hence that of the starting material. Although not mentioned in Mislow's review, this would also be a possible method to determine enantiomeric purity *via* a measurement of the optical rotation of the product (provided of course that the absolute rotation of the product was known).

#### 1.2.12.2 *Calorimetric Method*

Pure enantiomers have identical melting points, while racemates melt at some different temperature. This forms the basis for the differential microcalorimetric method of Fouquey and Jacques.<sup>136</sup> Generally, racemic forms are either *racemic compounds* (1 : 1 compounds of the enantiomers) or they are *conglomerates* (equimolar mixtures of crystals of the pure enantiomers). With either type of racemic mixture, this method, described by Raban & Mislow,<sup>137</sup> can be used to determine enantiomeric purity.

#### 1.2.12.3 *Isotope Dilution Analysis*

Isotope-dilution analysis was first described in 1932, but it was not until 1959 that the technique was applied to the determination of enantiomeric purity. The method is described by Andersen *et al*<sup>138</sup> and can be summarised as follows.

Firstly, a test sample is mixed with a sample of the same compound, but which is isotopically labelled and of known enantiomeric purity (usually a racemate). From this mixture a sample of known enantiomeric composition, often a racemate is isolated, typically by crystallisation. The isotopic content is measured by scintillation counting, MS or NMR. This is used to calculate the isotopic dilution and hence the enantiomeric purity of the original test sample.

#### 1.2.12.4 *Stereoselective Biosensor Techniques*

Biosensor technology is a very promising area that uses a probe which incorporates a biological component as the key functional element in a transduction sequence.<sup>139</sup> The biological component can be of two general types. The affinity type binds to an analyte with some subtle charge effect or conformational change in the bioreagent adduct. Transduction of the binding event is often difficult, relying on the detection of change of the biolayer charge, thickness, refractive index, viscosity, mass or heat. The catalytic type of biosensor involves analyte degradation which can make transduction more facile, typically using electrochemical or optical detection.

Because the biological component is often chiral (*e.g.* an enzyme) stereoselective analysis is clearly possible. A calorimetric biosensor has been devised by Hundek *et al*<sup>140</sup> which uses two enzymes, one which converts both analyte enantiomers, the other converts only one, allowing simultaneous determination of total analyte concentration and enantiomer ratio. Other workers have extended biosensor technology to provide stereoselective detection for chromatography. A typical example described the use of  $\alpha$ - or  $\beta$ -hydroxysteroid dehydrogenase immobilised in a post-column reactor.<sup>141</sup> The enzyme catalysed the oxidation of analyte hydroxysteroid with reduction of nicotinamide adenine dinucleotide (NAD) to the strongly fluorescent and easily detected reduced form (represented as NADH).

#### 1.2.12.5 *Radioimmunoassays*

Another method utilising a biochemical process was briefly noted by Lough<sup>142</sup> in his chapter on 'other techniques'. He cites examples of such assays for the determination of warfarin, ephedrine, and pentobarbital, but points out that the synthesis of a suitable

immunogen is seldom simple, and that it is difficult to avoid some cross-reaction with the opposite enantiomer and metabolites or other closely structurally-related compounds.

#### *1.2.12.6 Complexation with a Chiral Fluorescent Agent to form Diastereoisomeric Complexes*

Another interesting approach was recently reported by Parker *et al*<sup>143</sup> which relies upon the fluorescence which arises when a diastereoisomeric complex is formed between a fluorescent acid in its excited state and a non-fluorescent base. Complexes formed from a homochiral fluorescent acid and the two enantiomers of a base may have differing stabilities, in which case the fluorescence obtained will be proportional to the enantiomeric purity of the base.

#### *1.2.12.7 Chiral Derivatisation to Produce Diastereoisomers with Different Fluorescence-Quenching Abilities*

A related method was recently reported by the same group<sup>144</sup> which is based on the quenching of fluorescence which may occur when a diastereoisomeric complex is formed between a fluorescent acid in its excited state and a non-fluorescent base. Complexes formed from a homochiral fluorescent acid and the two enantiomers of a base may have differing stabilities. If the base has a quenching effect, then this will be proportional to the enantiomeric purity of the base.

### **1.3 PHILOSOPHY OF THIS RESEARCH**

#### **1.3.1 Aims and Strategy**

There is continuing interest in organosilicon chemistry at the Open University. The aim of the current research project was to prepare a chiral organosilicon reagent for analytical purposes. A range of halosilanes, chiral by virtue of an asymmetrically substituted carbon or silicon atom were considered. These halosilanes would be used to derivatise

nucleophilic compounds, principally alcohols and amines, prior to analysis of the diastereoisomeric derivatives by GC, HPLC, CE or NMR. Chlorosilanes are very commonly used in GC, which generally reduce the polarity of an analyte, and increase its volatility and thermal stability.<sup>145</sup> Silylation also assists in mass spectrometric analysis, and this was a valuable tool available at the Open University. Primary alcohols are more easily silylated than other nucleophiles, and are readily silylated by one of the most common, though least powerful reagents, trimethylchlorosilane (TMCS). A range of more reactive reagents is available, described in detail by Evershed.<sup>146</sup>

### 1.3.2 Brief comments on C<sub>2</sub>-Symmetric Chiral Auxiliaries and Reagents

In order to achieve chiral discrimination, chromatographic stationary phases or reagents need not be asymmetric, but must be dissymmetric, *i.e.* having no mirror or inversion symmetry.

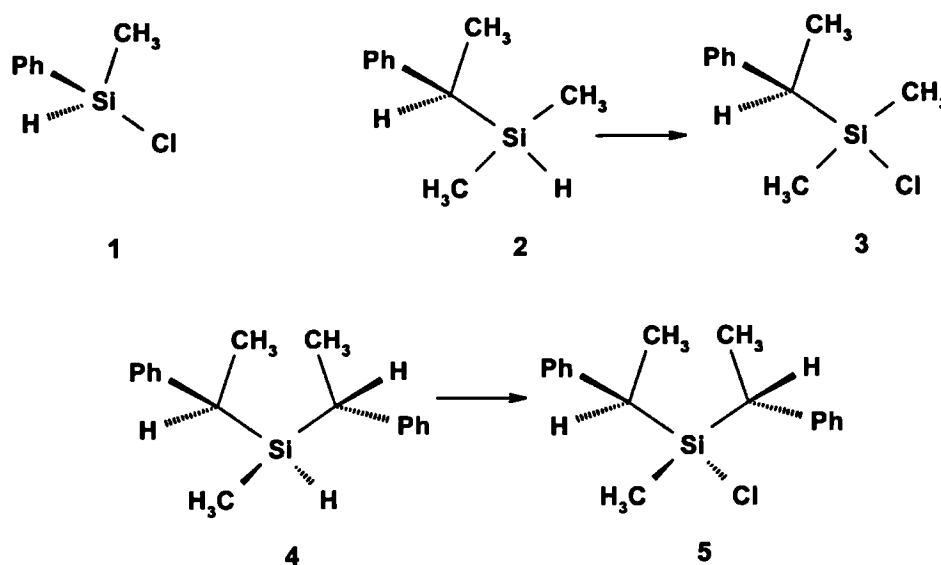
The use of helical polymers in chromatographic chiral separations has already been noted. The use of C<sub>2</sub>-symmetric chiral auxiliaries was the subject of a thorough review by Whitesell.<sup>147</sup> One important point made in this review is that many of the reagents are not C<sub>2</sub>-symmetric in the strict sense, but have a C<sub>2</sub>-component. This is particularly relevant to this thesis and is developed in the next section.

### 1.3.3 Choice of Chlorosilane Reagents for this Work

#### 1.3.3.1 *Acyclic Silicon Compounds*

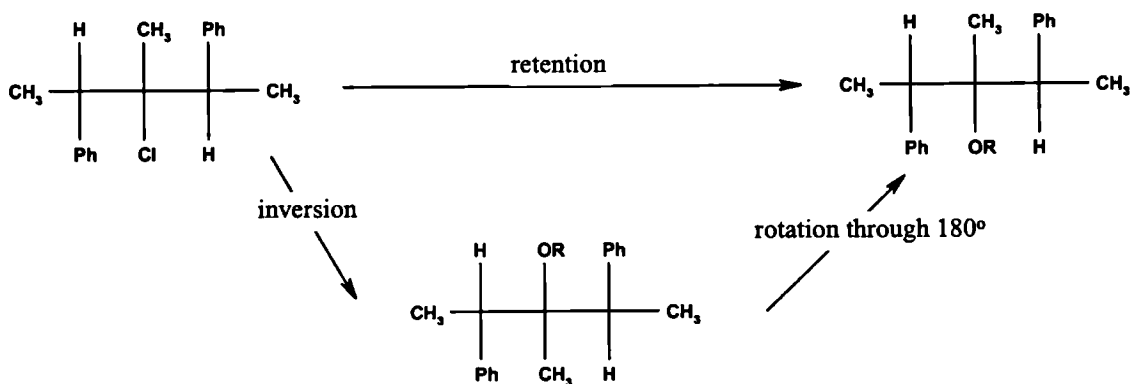
Chlorosilane reagents were selected with -Ph, -CH<sub>3</sub> and -H as the three different groups in the chiral moiety, positioned in different positions with respect to the silicon atom as shown in Scheme 1.2. The first of these, chloromethylphenylsilane (1) could be obtained in racemic form. The other chiral chlorosilanes could be prepared in two steps. Firstly, Grignard reaction of the racemic alkyl halide with the appropriate chloro- or dichlorosilane produces a silane. This is then chlorinated to give the required chlorosilane. In this way, (1-bromoethyl)benzene could be reacted with chlorodimethylsilane to give 1-phenylethyldimethylsilane (2), which is readily chlorinated to yield

1-phenylethylchlorodimethylsilane (**3**). Similarly, (1-bromoethyl)benzene could be reacted with dichloromethylsilane to give bis(1-phenylethyl)methylsilane (**4**) which is chlorinated to yield bis(1-phenylethyl)chloromethylsilane (**5**)



Scheme 1.2 Proposed acyclic chiral chlorosilane reagents and their precursor silanes where appropriate

As distinct from substitution at carbon, substitution at silicon may proceed either with inversion, or with retention of configuration, or with a combination of both. The mechanism of nucleophilic attack at silicon was recently reviewed by Bassindale and Taylor.<sup>148</sup> While reagent **1** may be expected to suffer from racemisation before or during the course of reaction, chlorosilanes **3** and **5** would be far less prone to such a fate. Whether the reaction of the latter reagents proceeds with inversion or retention of configuration *at silicon* does not affect the stereochemical outcome. In the case of chlorosilane **5**, taking the example above where the two  $\text{PhCHCH}_3\text{Si-}$  groups have the *R* configuration, the product of the reaction with retention at silicon can be rotated through  $180^\circ$  to become identical to the inversion product, as shown in Scheme 1.3.



Scheme 1.3 Mechanism of substitution at silicon (retention or inversion of configuration) produces identical product of etherification

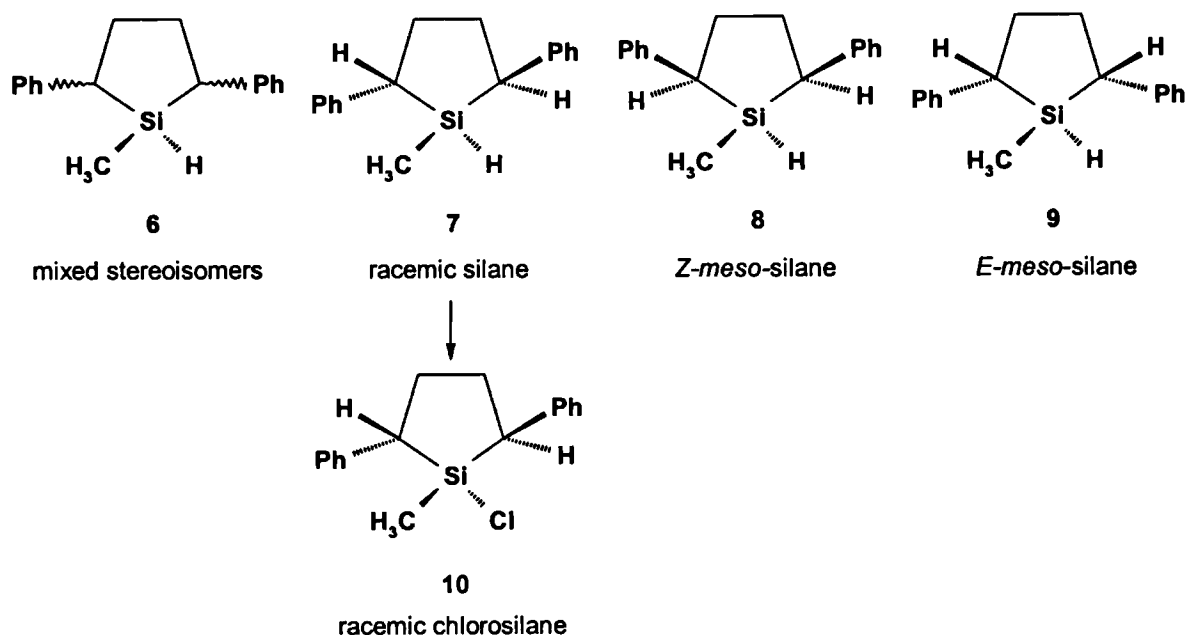
All the chlorosilane reagents used in this study were racemic, the emphasis being on preparation and separation of diastereoisomeric products.

#### 1.3.3.2 Cyclic Silicon Compounds

A potential cyclic chlorosilane reagent for this project was based on the novel silane precursor, 1-methyl-2,5-diphenylsilacyclopentane, which exists in four stereoisomeric forms. The anticipated procedure for the preparation of this compound would be expected to produce a mixture of the stereoisomers of 1-methyl-2,5-diphenylsilacyclopentane (6). The precursor of interest in this work was the racemate (2*R*,5*R* and 2*S*,5*S*)-1-methyl-2,5-diphenylsilacyclopentane (7). The two *meso*- isomers, *i.e.* the (1*R*,2*R*,5*S*)- and the (1*S*,2*R*,5*S*)- isomers were designated 8 and 9.

As with the acyclic silanes, chlorination of the silane 7 generates the chlorosilane, in this case, 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10).

These structures are shown in Scheme 1.4.



Scheme 1.4 Cyclic chlorosilane and precursors

Again, it is important to note that the silane, chlorosilane and product silyl ethers have C-centred, rather than Si-centred asymmetry and thus the asymmetry is independent of the stereochemistry at the silicon atom.

This reagent provides many of the advantages and meets most of the requirements for a good chiral derivatisation reagent for GC (sections 1.2.1.2-3 and 1.2.5.2). Factors which are particularly relevant in the case of this reagent were discussed by Skidmore<sup>61</sup> and Halpern.<sup>149</sup>

- The structural rigidity of the reagent at the chiral centre (silicon) and the proximity of this centre to the site of attachment of the analyte, maximises the likelihood of a good diastereoisomeric separation.
- The presence of a polar or polarisable group close to the functional group is desirable because it facilitates hydrogen bonding or  $\pi$ -orbital overlap between the diastereoisomers and the stationary phase.
- The linking group between the reagent and analyte can influence the diastereoisomeric separation. For instance, a carbonyl linking group was found not to be essential for diastereoisomeric separation, and amides often give better

separations than esters. The reviews cited in this introduction refer mostly to the commonly prepared diastereoisomeric derivatives such as amides and esters, and those less frequently prepared, such as carbonates, carbamates and hydrazones.

However, there has been (understandably) very little attention to the formation of diastereoisomeric ethers for the purpose of enantiomeric analysis, and a survey of the literature indicates that there have been no reports of the use of diastereoisomeric silyl ethers in GC in this regard. A study by Rimmer and Rose<sup>150</sup> included the preparation of diastereoisomeric ethers which provided good gas chromatographic separations. The reagents in this study were mostly esters or lactones, although these groups were not associated with the derivatisation process. Whether the ester function was helpful in the diastereoisomeric discrimination is not known for certain, but it can be assumed that it did not constitute a major chromatographic binding site for three reasons. The GC phases used were of low polarity, so would not be expected to interact strongly with the ester group. The ester group was four atoms removed from the analyte chiral atom and the diastereoisomers would have been less effectively separated had the ester-stationary phase interaction predominated as the chromatographic retention mechanism. Finally, the authors concluded that the alkyl chain (from the alcohol used to prepare the ether) played a significant part in the retention mechanism. On this basis it would appear that the diastereoisomeric ethers referred to in Rimmer and Rose's paper were separated from each other as a result of differences in the region of the two chiral centres on either side of the ether link. The presence of the aromatic groups was expected to provide two advantages as an analytical derivatisation reagent. Firstly, the aromatic groups would be close to the nucleophile radical and were hoped to aid in the process of discrimination by enhancing the difference between the two diastereoisomers. This could occur as a steric interaction or as a charge transfer interaction. Secondly, the aromatic group provides a chromophore for detection, especially for HPLC analysis of the diastereoisomers. One factor that favoured diastereoisomeric separation noted by Halpern was a large size difference between groups attached to the asymmetric centre of the reagent. The chlorosilane **10** is lacking in this respect, in that the silicon atom has, apart from the chlorine atom which will be replaced by the linking oxygen atom, a methyl group and *two* CHPh- groups, which only differ in their



orientation relative to the substituents at silicon. However, looking at the overall stereochemical structure in the region of the chiral centres from the reagent and the analyte, particularly if there is any conformational preference in the diastereoisomeric derivatives, it is easy to visualise a distinct difference between the diastereoisomers.

The use of chlorosilanes, particularly as derivatisation reagents for GC, is well documented, and was reviewed by Evershed.<sup>146</sup> This review covers many of the common derivatisation procedures used in silylation, with reference to the reactivity of reagents, reduction of polarity to improve characteristics for GC, incorporation of a probe for MS detection (characteristic ionic fragments from silicon-containing derivatives), and stability to solvolysis of silyl ethers substituted at silicon. This reagent was expected to provide derivatives with reasonable stability with respect to trimethylsilyl (TMS) ethers, being more similar to *tert*-butyldimethylsilyl (TBDMS) ethers, which are approximately 10<sup>4</sup> times more stable to hydrolysis.<sup>151</sup>

The silicon methyl group situated close to the chiral centre of the derivatising group was expected to provide a useful probe for NMR. The low chemical shift of the SiCH<sub>3</sub> group enhanced the selectivity of the method because the signal is removed from the more populated regions of the spectrum, and could be observed as the <sup>1</sup>H, <sup>13</sup>C or <sup>29</sup>Si signal.

#### *1.3.3.3 Related Studies Of Silylating Reagents For Enantiomeric Analysis By Chromatography*

A survey of the literature on studies similar to the subject of this research and on related preparations was carried out. This was extended with a thorough CAS On-line search in attempt to reveal any comparable studies. In total, only three papers dealing with the separation of silyl ether diastereoisomers by chromatography were located. The earliest of these was a comparison of the GC separations of symmetrically substituted dichiral ethers, alkoxysiloxanes and disiloxanes carried out by Feibush and Spialter.<sup>73</sup> This work provides a useful insight into the difficulty inherent in this approach. The diastereoisomeric ethers, alkoxysiloxanes and disiloxanes were of the form RCHCH<sub>3</sub>-O-CHCH<sub>3</sub>R, RCHCH<sub>3</sub>-O-SiHCH<sub>3</sub>R, RSiHCH<sub>3</sub>-O-SiHCH<sub>3</sub>R, where R = various pentyl substituents. Without

exception, the ease of separation decreased across this series, with the mean separation factor ( $\alpha$ ) falling significantly from 1.09 for the ethers to 1.02 for the alkoxyloxanes, while no separation was observed for the disiloxanes. Although in the early days of capillary GC, Feibush, using a 50m column, was able to observe separations having  $\alpha$  values as low as 1.01. I hoped that the proposed reagent, 1-chloro-1-methyl-2,5-diphenylsilacyclopentane, would provide adequate selectivity for analytical GC use.

As briefly noted in Section 1.2.5.2, two papers were published in 1990 by Kaye and Learmonth<sup>43</sup> and by Brooks *et al*<sup>74</sup> which commented on the absence of any investigation into the potential use of chiral organosilicon reagents for enantiomeric analysis by GC and a search carried out for this study (in 1996) shows that this still appears to be the case, and that this conclusion can be extended to all forms of chromatography.

A recent search immediately before submission of this thesis confirmed that there are no references in the literature to 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**) or the precursor silane (**6**).

Kaye prepared silyl acetals similar to those made for NMR studies by Chan *et al*,<sup>42</sup> discussed in Section 1.2.3.3. Menthol was used to generate chloro(menthyloxy)dimethylsilane from which diastereoisomeric silyl acetals (Figure 1.13) were formed from 2-butanol, 2-pentanol, 2-octanol and 1-phenylethanol. The borneol analogue with 1-phenylethanol was also prepared.

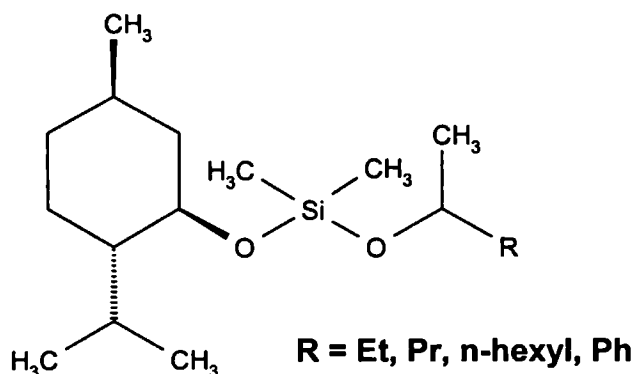


Figure 1.13 Diastereoisomeric silyl acetals prepared from menthol

Gas chromatographic separation of the diastereoisomers was achieved, but, as shown in Table 1.1, the separation of derivatives was poor, the peaks being only partially resolved despite the authors having resorted to the use of a 60 m GC column. The diastereoisomers of the borneol analogue of the 1-phenylethanol derivative were no better separated.

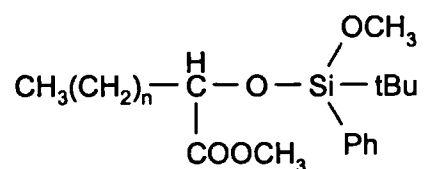
R group (see figure 1.13)	Column length (m)	Retention of diastereoisomers (minutes)	Resolution ( $R_s$ )	Selectivity ( $\alpha$ )
Ethyl	60	Not reported	No separation	-
Propyl	60	Not reported	No separation	-
<i>n</i> -hexyl	30	35.60, 35.78	0.69	1.005
	60	71.63, 71.84	0.75	1.003
Phenyl	30	41.14, 41.35	0.80	1.005
	60	84.37, 84.70	0.88	1.004

Table 1.1 Gas chromatographic data for diastereoisomeric silyl ether derivatives based on menthol prepared by Kaye and Learmonth.<sup>43</sup>

The chromatographic resolution achieved in this work was considerably less than is required for quantitative analysis, where a value of  $R_s=1.5$  is generally regarded as a minimum acceptable resolution (*baseline resolution*).

On the simple basis that fewer bonds between the chiral centres of a pair of two centre diastereoisomers leads to better separation, this result is fairly promising, since the silyl ethers formed from chlorosilane **10** and, for instance, chiral secondary alcohols would have fewer bonds between the centres.

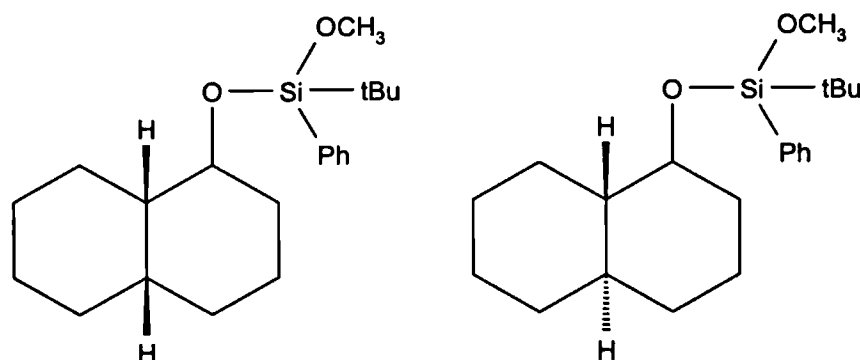
Brooks' group prepared diastereoisomeric silyl ethers from *tert*.-butylmethoxyphenylsilyl bromide.



The resulting *tert*.-butylmethoxyphenylsilyl ethers of methyl 2-hydroxylaurate ( $n=9$ ) and methyl 2-hydroxy-myristate ( $n=11$ ) were just baseline-resolved by GC.

Figure 1.14 Diastereoisomeric silyl acetals prepared by Brooks *et al.*<sup>152</sup>

Similarly, the diastereoisomeric products of the reaction of *tert*-butylmethoxyphenylsilyl bromide with racemic *trans*, *trans*- $\alpha$ -decalol or racemic *cis*, *cis*- $\alpha$ -decalol were baseline-resolved by GC.

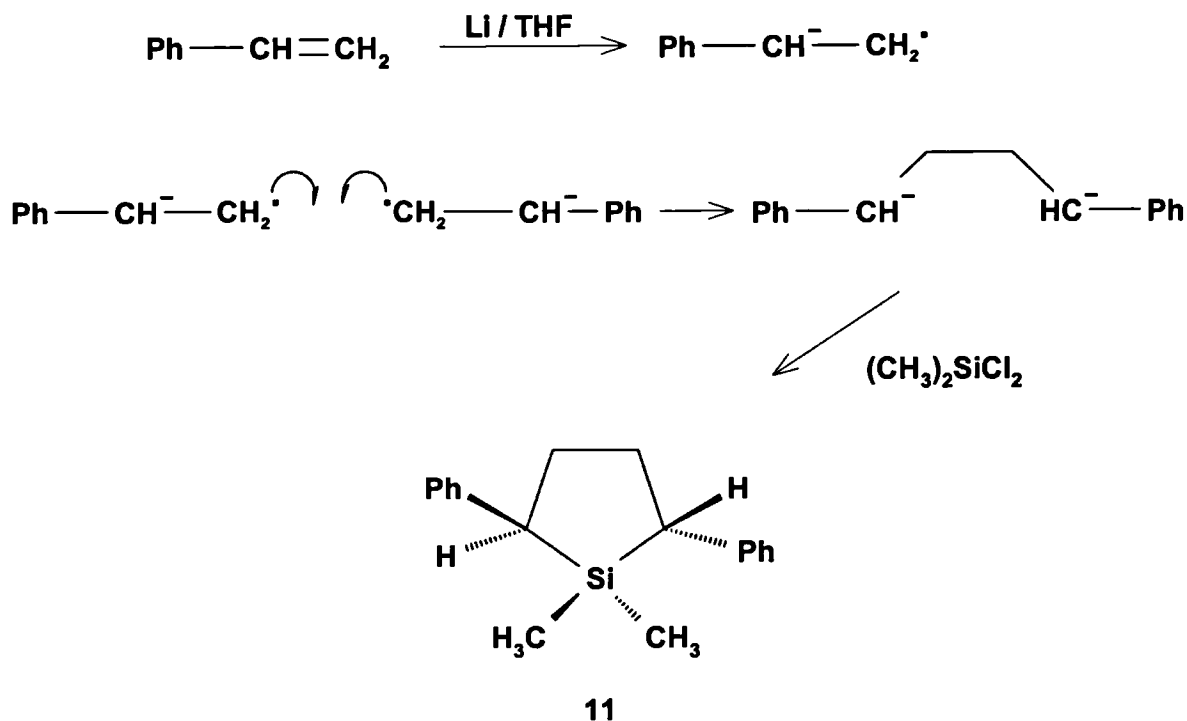


#### 1.3.3.4 Preparations of Related Silacyclopentane Compounds

Similar silacyclopentane compounds have been prepared, mostly as potential chiral auxiliaries, by Nefedov,<sup>153, 154</sup> Weyenberg,<sup>155</sup> Wells and Franke,<sup>156, 157</sup> Dang *et al*,<sup>158</sup> Barrett *et al*<sup>159</sup> and Bradley.<sup>160</sup>

Compounds of this type were originally prepared by Nefedov from styrene or related compounds with a dichlorosilane in the presence of an alkali metal. In this way, compounds such as 1,1-dimethyl-2,5-diphenylsilacyclopentane (11) were prepared.

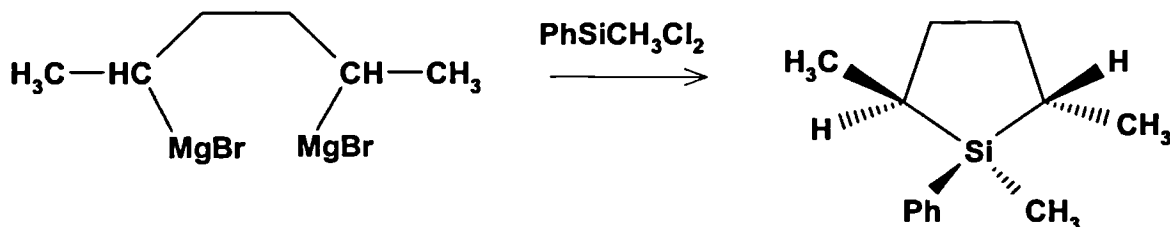
Similar work by Weyenberg<sup>155</sup> led to the conclusion that the reaction proceeds *via* electron transfer from the alkali metal to the alkene. The resulting radical anion dimerises (electron spin resonance measurement shows no unpaired electrons)<sup>161</sup> to form the more stable dicarbanion and the short-lived organodialkali products are then trapped by the chlorosilane, as shown in Scheme 1.5.



Scheme 1.5 Formation of 1,2-dimethyl-2,5-diphenylsilacyclopentane from styrene.<sup>153</sup>

Weyenberg demonstrated that lithium gave a higher yield than sodium (71% vs. 40%). Furthermore, a deficiency of styrene resulted in a preference for the 3,4-diphenyl substituted compound. For instance, equimolar styrene/dichlorodimethylsilane mixtures gave no 2,5-diphenyl substituted compound.

Wells and Franke's preparation utilised a diGrignard reagent, which was cyclised with the appropriate dichlorosilane as shown in Scheme 1.6.



Scheme 1.6 Cyclisation *via* diGrignard reagent to form silacyclopentane.<sup>156</sup>

Dang *et al* recently reported a modified Grignard method, having improved the yield by adding the chlorosilane and alkyl dibromide together to magnesium. Following the

preparation of the 1-chlorosilacyclopentyl compound, the silyl ether was formed with (2*S*)-1,1,2-triphenylethane-1,2-diol. The resulting diastereoisomers were resolved using a combination of crystallisation and chromatography to provide a crystalline product, the absolute configuration of which was determined by X-ray diffraction crystallography. Reduction with lithium aluminium hydride yielded the silane with high enantiomeric purity. This paper only refers to 2,5-*dialkyl* silacyclopentyl compounds, whereas, for the reasons discussed above, the present study focused on *diaryl* analogues.

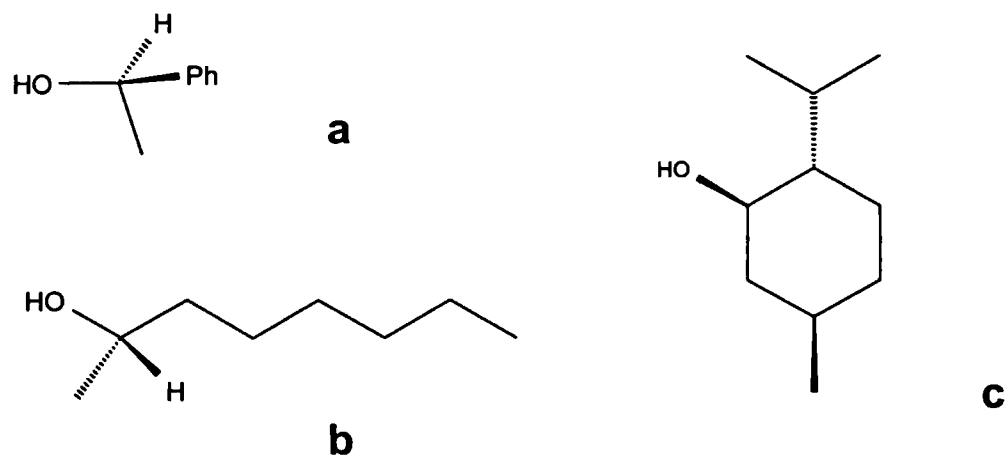
A similar Grignard method to prepare 1-methyl-2,5-diphenylsilacyclopentane was attempted by Xu<sup>162</sup> but failed because of the difficulty in forming the diGrignard intermediate from the dibromide, which rearranged to produce styrene.

Since the commencement of this research, Barrett,<sup>159</sup> citing the procedure of Araki *et al*,<sup>163</sup> (which was essentially similar to that of Nefedov), successfully prepared 1-allyl-2,5-diphenylsilacyclopentane. As with all the methods employed, a mixture of stereoisomers was obtained. Barrett was unable to resolve the required *trans*- isomers from the two *meso*-forms by extensive chromatography or fractional distillation. Eventually, the racemic *trans*-isomers were obtained by chromatography of the chromium hexacarbonyl complexes. Decomplexation yielded the allylic product with an overall yield of 11%. The next step was conversion to the chlorosilane. This was one of the target compounds of my research, but it appears that the silane that I intended to prepare using the Nefedov procedure with styrene, alkali metal, and dichloromethylsilane, *i.e.* 1-methyl-2,5-diphenylsilacyclopentane is still (November 2001) an unreported compound.

#### 1.3.4 Choice of Model Alcohol Reagents for this Work

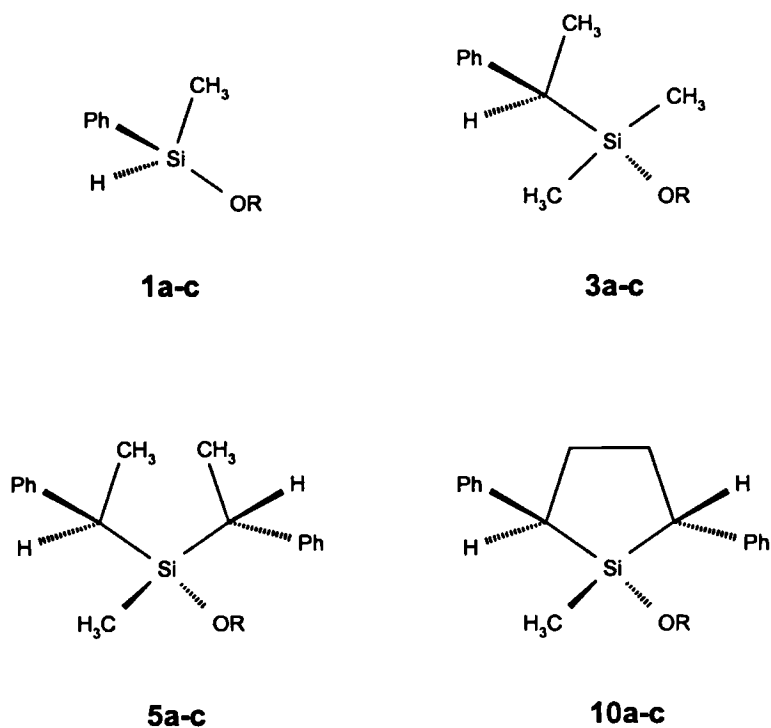
Three general types of chiral alcohol were selected for the initial study, in order to investigate the utility of different groups adjacent to the chiral centres in creating sufficient

distinction between diastereoisomeric products to effect separation by chromatography. The three alcohols selected as being typical of these groups, shown in Scheme 1.7, represent those with an aromatic group, an alkyl chain or a bulky group close to the chiral centre bearing the hydroxyl group.



Scheme 1.7 Model alcohols selected for this research

The alkoxyasilanes were numbered according to their parent chlorosilane, as outlined in Scheme 1.8.



Scheme 1.8 Diastereoisomeric alkoxyasilanes investigated in this work

### 1.3.5 Notes On Some Conventions Used

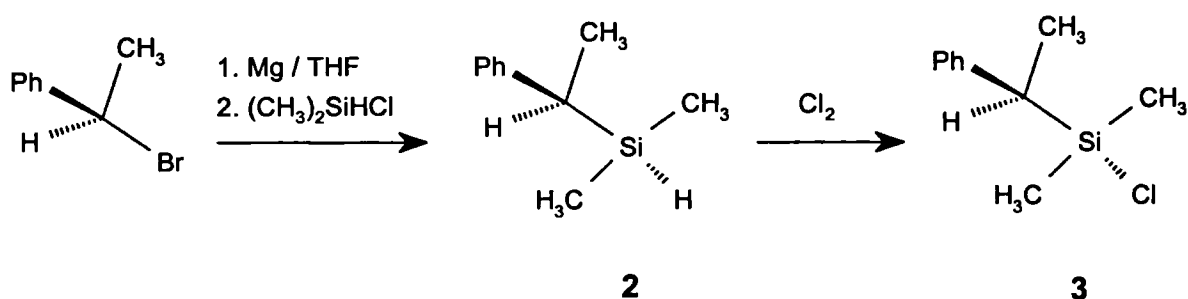
For convenience, structures have been shown with their *relative* stereochemistry. Where figures are intended to relate to *absolute* configuration this is indicated in the text.



## CHAPTER 2

### PREPARATION OF ACYCLIC CHLOROSILANES

#### 2.1 1-PHENYLETHYLCHLORODIMETHYLSILANE (3)



Preparation of 1-phenylethyldimethylsilane (**2**) was accomplished by the Grignard route shown. The structure of **2** was determined by NMR and EIMS. The product was accompanied by the formation of the dimeric Wurtz-type coupling product, 2,3-diphenylbutane. This is not without precedent; these dimeric by-products have been reported in similar preparations<sup>164, 165</sup> and is a general problem with the preparation and use of benzylic (or allylic) Grignard reagents.<sup>166</sup> Evidence for the formation of these two diastereoisomeric by-products in this work came from NMR<sup>164</sup> and a satisfactory EIMS (agreement with library spectrum).

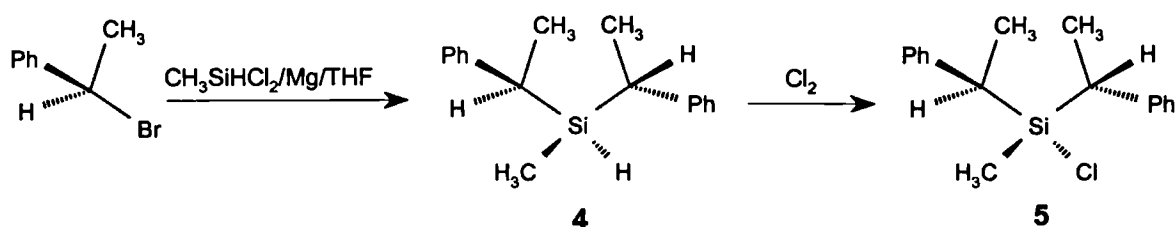
Other by-products which were apparent from the GC/EIMS were ethylbenzene and styrene. These were present at *ca.* 2% of the total GC peak area.

The ratio of the desired product to the two diastereoisomeric dimeric impurities was, respectively, 36 : 25 : 39 according to GC and 27 : 27 : 46 by NMR. These impurities were

completely removed by distillation. On the basis of the chlorosilane added, the yield was 27%. Later work (preparation of **4**) showed that the proportion of dimeric impurities could be reduced by placing the chlorosilane with the magnesium before the addition of (1-bromoethyl)benzene; the Grignard reagent is therefore generated in the presence of excess chlorosilane.

Chlorination of the silane produced 1-phenylethylchlorodimethylsilane (**3**) in high yield. The reaction was conveniently carried out in an NMR tube and its progress monitored by the disappearance of the silane proton signal. After distillation, NMR analysis of the product was consistent with that expected for **3**.

## 2.2 BIS(1-PHENYLETHYL)CHLOROMETHYLSILANE (**5**)



In the preparation of bis(1-phenylethyl)methylsilane (**4**), the Grignard reagent was formed in the presence of dichloromethylsilane, which limited the amount of 2,3-diphenylbutane dimers produced to 20%, as determined by GC/MS, resulting in a 64% yield of the required silane. Silane **4** had a higher boiling point than **2**, as expected. The 2,3-diphenylbutane impurity had an intermediate boiling point and was therefore more difficult to remove from **4** by distillation. Distillation was also hampered by the ready solidification of the condensate such that the by-product dimer content was only reduced to 14%. As an example, the EIMS of **4** is shown in Figure 2.1.

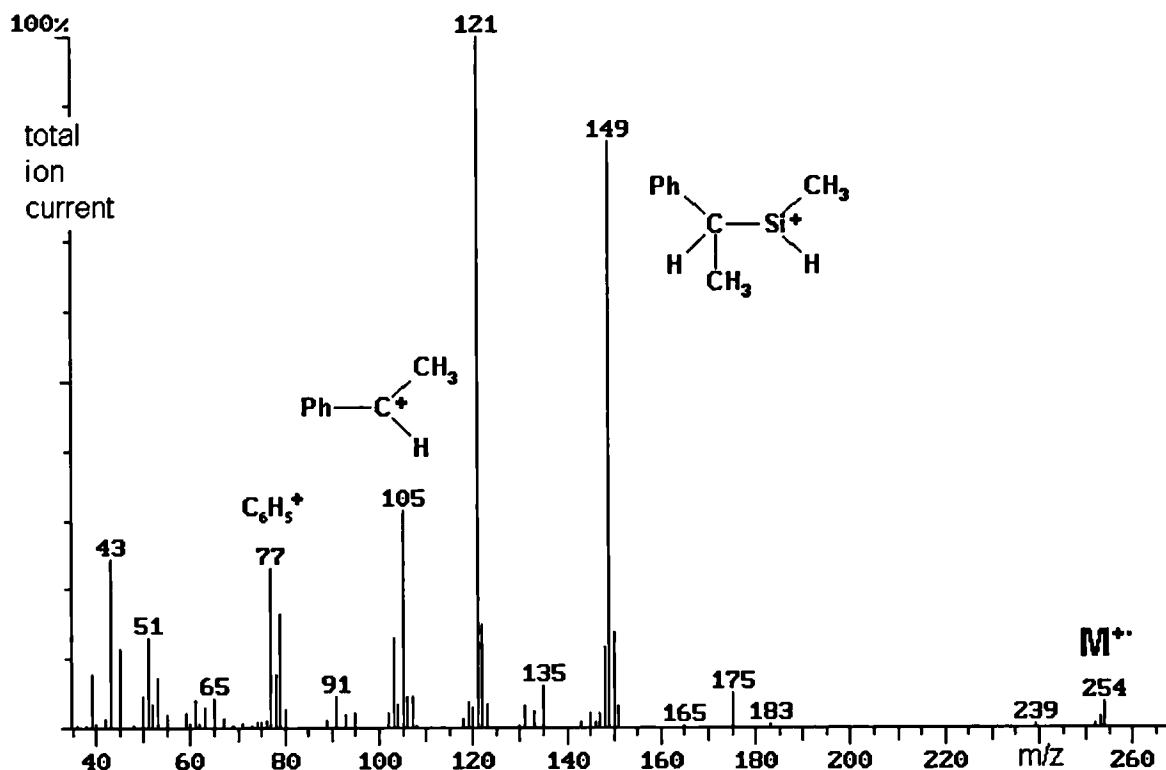
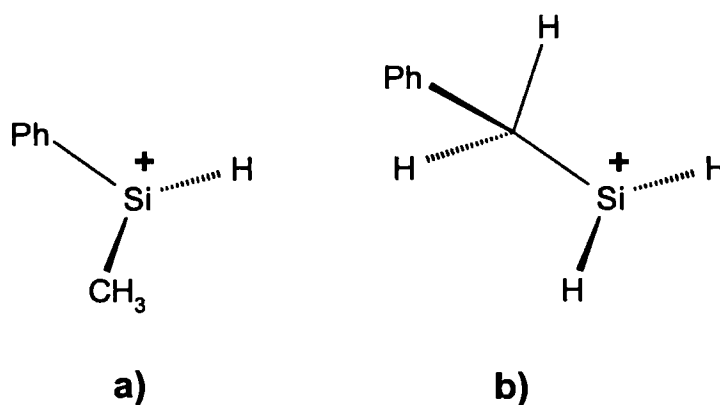


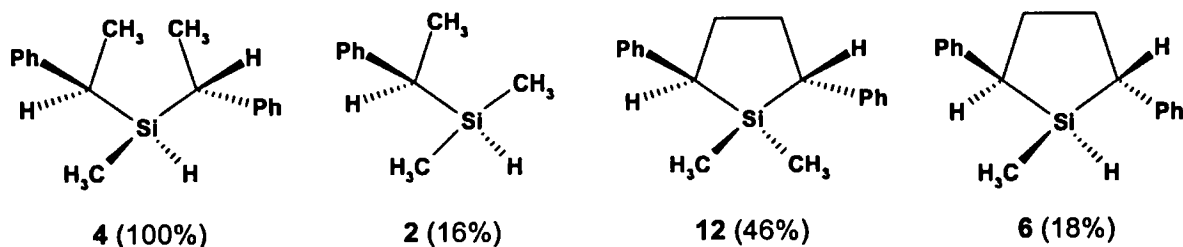
Figure 2.1 EIMS of bis(1-phenylethyl)methylsilane (4)

An interesting feature of the EIMS of 4 (Figure 2.1) was the base peak at  $m/z$  121, which could only reasonably have the molecular formula  $C_7H_9Si$ . This ion was expected to have one of the structures shown in Scheme 2.1, both of which require a rearrangement, more so for a) than for b).



Scheme 2.1 Possible structures for ion with  $m/z$  121

The ion with  $m/z$  121 may have had the same structure as that observed to a far lesser extent in the EIMS of 2 (16 % RA) and in the EIMS of the cyclic compounds 12 (46 %) and 6 (18%). These compounds are shown in Scheme 2.2.

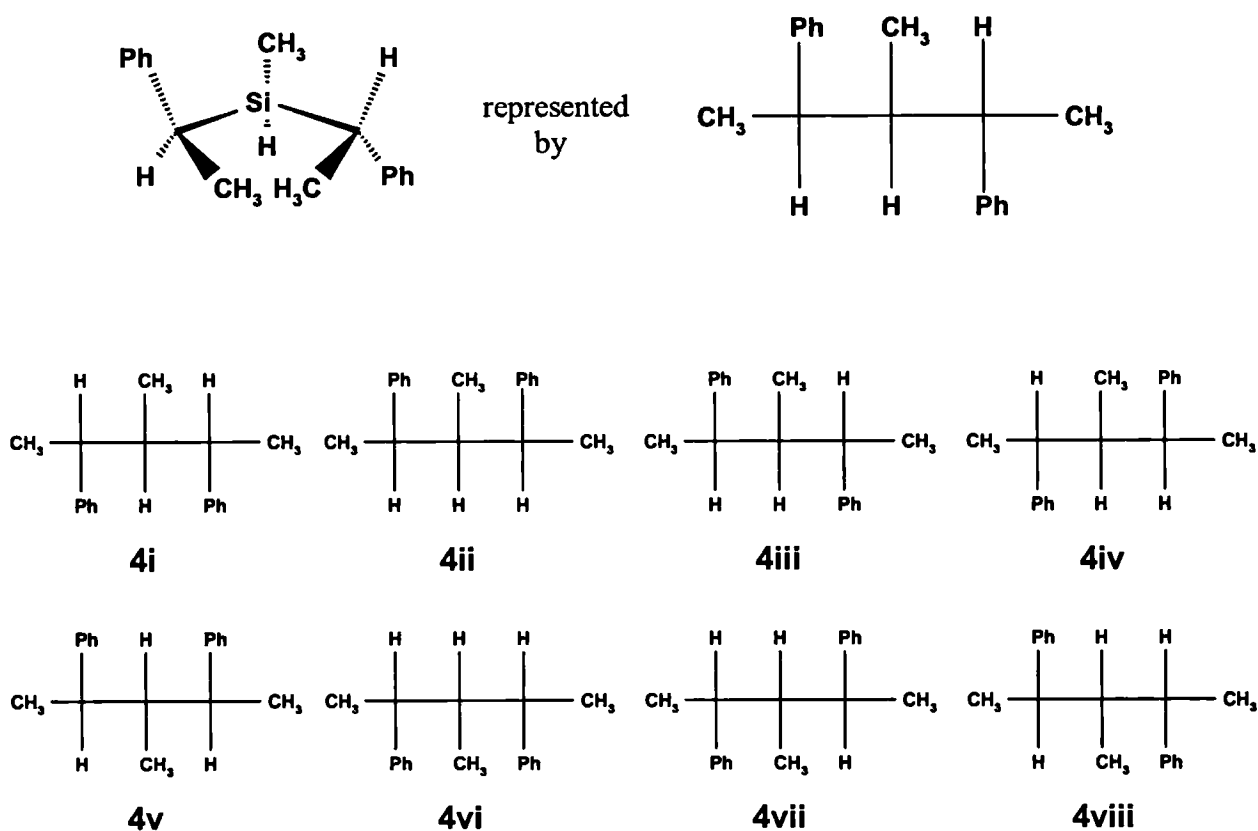


Scheme 2.2 Compounds related to **4** and the relative abundance of fragment ion with  $m/z$  121 in their EIMS (RA in parentheses)

The structure in Scheme 2.1a) was proposed by Maruca *et al*<sup>167</sup> in their study of **12** and seems to be the most likely in this case.

The abundant ion at  $m/z$  149 was genuine (*i.e.* not that commonly associated with phthalate plasticisers) and was presumably due to  $[\text{PhCHCH}_3\text{SiHCH}_3]^+$ .

The product **4** has three chiral centres. Using the Fischer-type representation shown below, the eight structures that can be drawn are illustrated in Scheme 2.3.



Scheme 2.3 The eight structures that can be drawn for silane **4**. The lower set are mirror images of the upper set.

Stereochemical definitions and considerations have been given in many texts, especially those of Testa,<sup>168</sup> Mislow<sup>169</sup> and Gunstone.<sup>170</sup> Of the eight structures that can be drawn, four (4i, 4ii, 4v and 4vi) have a plane of symmetry (through the CH<sub>3</sub>-Si-H bonds). Because of this, their mirror images are identical (4i and 4v are *homomeric*, as are 4ii and 4vi). In these cases, although lying in the plane of symmetry, the silicon atom has four different substituents (CH<sub>3</sub>, H, an *R* phenylethyl moiety and an *S* phenylethyl moiety) and is said to be in a *pseudoasymmetric* position.<sup>171</sup> Considering structure 4i, inverting the configuration at silicon alone results in a different diastereoisomer, 4vi, also plane-symmetrical. Thus, two such *meso*-stereoisomers will exist. The other four structures are *disymmetric* (*i.e.* they have no reflection symmetry) and are therefore chiral. However, because the carbon centres have the same configuration, inversion at silicon results in the identity (*i.e.* 4iii  $\equiv$  4viii and 4iv  $\equiv$  4vii), so these four structures reduce to one racemate. There are therefore two symmetric *meso*-forms (4i and 4ii) and two enantiomeric forms (4iii and 4iv). The upper set in Scheme 2.3 therefore represent the only four "real" structures which exist for 4.

As expected, the product was formed indiscriminately as three diastereoisomers, evidenced by the three partially resolved peaks in the GC analysis with ratios 1 : 2 : 1. The NMR spectrum showed a similar pattern for the SiCH<sub>3</sub> <sup>1</sup>H signals. The two CCH<sub>3</sub> groups in each isomer complicated the spectrum, being enantiotopic in the symmetric diastereoisomers and homotopic in the asymmetric diastereoisomer.

GC and NMR analysis showed that there was little difference between the isomer ratios of the distillate fractions, implying that distillation would be of little use in purifying the product diastereoisomers. A sample of the distilled product was found to have partially solidified (*ca.* 30% solid), with the appearance of crystallinity, under ambient conditions. However, NMR analysis showed that there was little difference between the isomeric compositions of the two phases. Normal-phase HPLC was used in an attempt to resolve the diastereoisomers of bis(1-phenylethyl)methylsilane. The compound was poorly retained on the column, and the isomers were not resolved.

The HPLC chiral stationary phase, Chiralcel OD, consisting of the 3,5-dimethylcarbamate of cellulose coated on 5  $\mu\text{m}$  spherical silica was more useful, resulting in a group of five peaks. Although these were very poorly resolved and scale-up would have been extremely laborious, sufficient material was produced to obtain GC/MS and NMR analyses. The GC/MS analysis confirmed that some isomeric separation had taken place. Whereas the NMR spectrum of the mixed isomers was extremely complex, the NMR spectra of the HPLC fractions, described in detail in Section 7.4.3, allowed a comprehensive assignment for each isomer.

The GC/MS showed that the first fraction from the chiral HPLC predominantly consisted of one of the two 2,3-diphenylbutane diastereoisomeric impurities. The  $^1\text{H}$  NMR was consistent with it being the (*RS,RS*)-diastereoisomer.<sup>164</sup>

The second fraction contained bis(1-phenylethyl)methylsilane (**4**) isomers, which gave two peaks in the GC, both having identical mass spectra. Of the three diastereoisomers of **4**, these were the two having extremes of chemical shift for the  $\text{SiCH}_3$  groups. It was possible to distinguish the sets of signals from each diastereoisomer in the fraction because they were present at slightly different concentrations. Thus, it was possible to deduce that, for each diastereoisomer, the two  $\text{CCH}_3$  groups were magnetically equivalent (being enantiotopic). These two observations, and the fact that in the NMR of the original diastereoisomer mixture the  $\text{SiCH}_3$  signals were each present at  $\frac{1}{4}$  of the total, all showed that the two diastereoisomers in this fraction were the two *meso*-isomers.

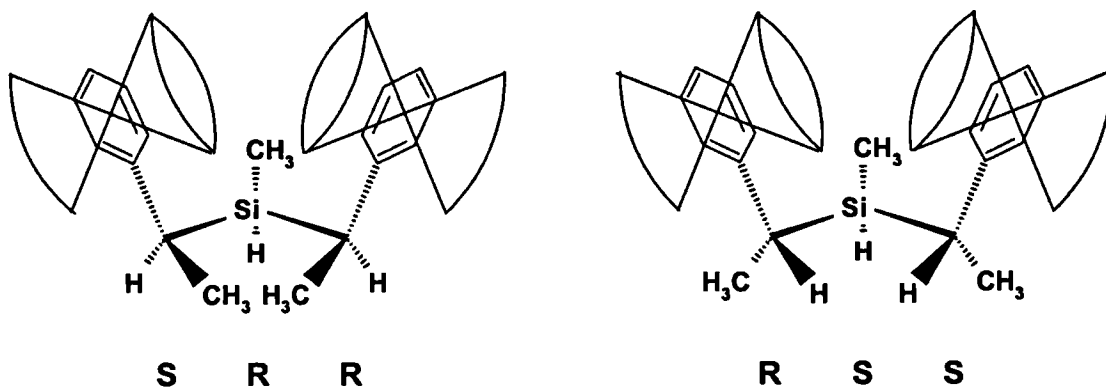
The two components which separated and eluted later on the chiral HPLC had identical GC retention times and mass spectra. The NMR spectra were also identical, differing from those of the *meso*-isomers, in that the two CH groups and the two  $\text{CCH}_3$  groups were clearly non-equivalent. These were therefore believed to be the resolved enantiomers.

As noted above, the two *meso*-isomers of **4** had extremes of proton chemical shift for the  $\text{SiCH}_3$  group. This was also true for the  $\text{SiCH}_3$  carbon chemical shifts, which were in the region of -9.20 to -10.08 ppm for the three diastereoisomers. The fact that the shifts were all at *ca.* -10 ppm suggested that the carbon atom was shielded by the phenyl ring. In the  $^1\text{H}$

and  $^{13}\text{C}$  COSY NMR, the  $\text{SiCH}_3$   $^1\text{H}$  and  $^{13}\text{C}$  shifts were correlated in inverse order of shift (e.g. the isomer with highest  $\delta_{\text{H}}$  had lowest  $\delta_{\text{C}}$ ). In one *meso*-isomer the  $\text{SiCH}_3$  protons were, on average, within the shielding cone of the phenyl ring ( $\delta_{\text{H}} = -0.26$ ). In the other *meso*-isomer ( $\delta_{\text{H}} = 0.04$ ) the  $\text{SiCH}_3$  protons were outside the shielding cone, but the  $\text{SiCH}_3$  carbon atoms were shielded to a greater extent. The shielding or deshielding of the proton or carbon nucleus would be influenced by conformational factors, principally the orientation of the phenyl ring with respect to the  $\text{SiCH}_3$  group, and the rotation about the  $\text{Si-CHCH}_3\text{Ph}$  bond.

The similarity of the diastereoisomers of **4** and those of **6** (shown in Scheme 2.2) means that it is convenient to relate them in terms of absolute configuration, but unfortunately the numbering system designated by the IUPAC name allocates different numbers to related atoms. To overcome this, and for the purposes of this part of the discussion only, the four compounds are described by the absolute configuration at each centre, in the order C-Si-C. For instance, compound **4i** in Scheme 2.3 would be referred to as the RSS isomer.

Shielding of the  $\text{SiCH}_3$  protons clearly occurred in one of the *meso*-isomers. Working with ball-and-stick models, and for simplicity only initially considering symmetric conformations, it can be seen that there is only a narrow range of  $\text{Ph-C-Si-CH}_3$  dihedral angles which allow this to occur. Taking the symmetric conformational extreme for each *meso*-isomer that allows greatest shielding of the  $\text{SiCH}_3$  group (identical orientation with respect to the phenyl rings), it is clear that one *meso*-isomer (the SRR isomer, structure **4ii**) suffers far more steric interaction between the two  $\text{CCH}_3$  groups than in the other (the RSS isomer, structure **4i**) as shown in Scheme 2.4. This can only be alleviated by conformational change, with loss of  $\text{SiCH}_3$  shielding by at least one of the phenyl rings. It is therefore likely that the *meso*-isomer with  $\delta_{\text{H}} = -0.26$  was the RSS isomer and the isomer with  $\delta_{\text{H}} = 0.04$  was the SRR isomer.



Scheme 2.4 Comparison of the two *meso*-isomers of **4** in the conformation that allows greatest shielding of the SiCH<sub>3</sub> group

A modified GC method (reduced temperature programme of 2°C/min) mostly resolved the *meso*-isomers (with  $\Delta t_R = 6$  s), the enantiomers having intermediate retention time.

Because of the difficulty of purifying the required racemate, a decision was taken to proceed with the unpurified product stereoisomers, in the hope that the complications that would arise would not be insurmountable.

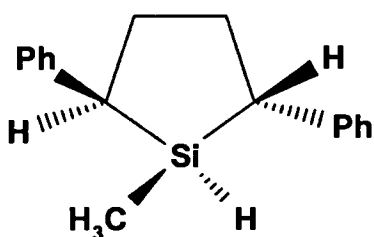
Bis(1-phenylethyl)chloromethylsilane (**5**) was smoothly prepared from this silane mixture in the same way as for 1-phenylethylchlorodimethylsilane (**3**).



## CHAPTER 3

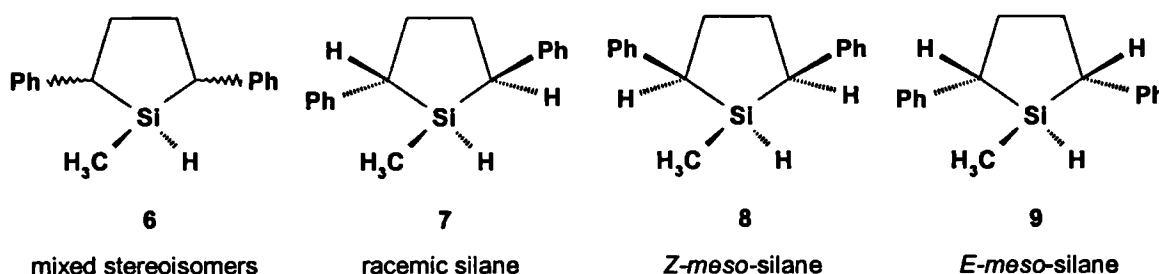
### PREPARATION OF 1-CHLORO-1-METHYL-2,5-DIPHENYLSILACYCLOPENTANE

#### 3.1 PREPARATION OF 1-METHYL-2,5-DIPHENYLSILACYCLOPENTANE (6)



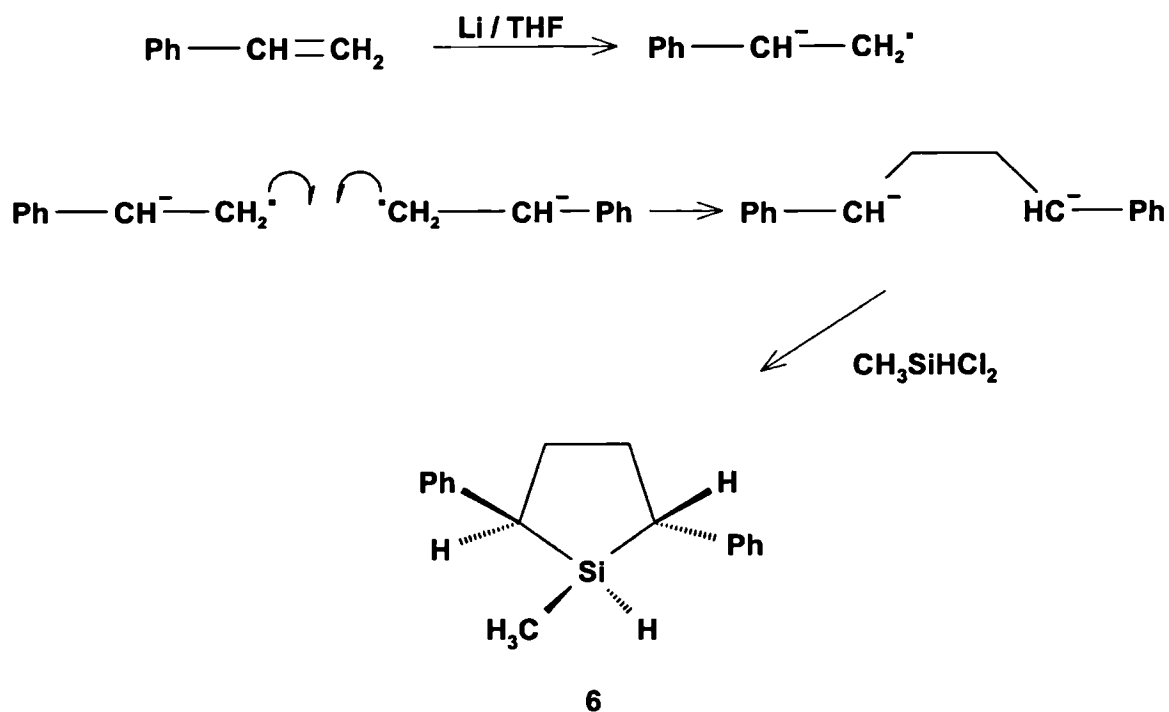
The stereochemistry of **6** is the same as that for **4**, because the symmetry elements are identical. There are therefore four stereoisomers: two *meso*-isomers and a pair of enantiomers.

The structures and their numbering were outlined in the introduction and are shown in Scheme 3.1.



Scheme 3.1 Structures and numbering of the cyclic silacyclopentane stereoisomers

The silacyclopentane (**6**) was prepared by coupling two moles of styrene using lithium, *via* a radical carbanion mechanism as described in Section 1.3.3.4, and then cyclised with dichloromethylsilane as shown in Scheme 3.2.



Scheme 3.2 Preparation of 1-methyl-2,5-diphenylsilacyclopentane (**6**)

### 3.1.1 Typical Small-Scale Preparation of 1-Methyl-2,5-diphenylsilacyclopentane (**6**)

The reaction was monitored by GC/FID and GC/MS to estimate the reducing concentration of styrene. GC was a useful guide to trends in the concentration of reagents and products, but could be misleading as it later became apparent that some products were not eluted.

NMR spectra of the crude product contained evidence of alkene signals (styrene), typically with a similar molar concentration as the product (**6**). However, the ratio of the aromatic signals to the sharp SiCH<sub>3</sub> signals of (**6**) was very large. When using similar reaction procedures with dichlorodimethylsilane as the trapping agent, Nefedov<sup>153</sup> reported the formation of a great deal of resinous material, characterised as a polymer having the formula (CH<sub>2</sub>CHPh)<sub>8</sub>(Si(CH<sub>3</sub>)<sub>2</sub>)<sub>6</sub>.

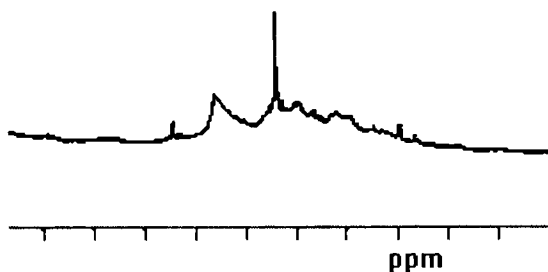


Figure 3.1  $^1\text{H}$  NMR of crude reaction product mixture

In the experiment currently described, the broad  $^1\text{H}$  NMR  $\text{SiCH}_3$  bands around 0 ppm (Figure 3.1) suggested that a silicon-containing polymer was a major by-product.

Solubility experiments were performed to devise a simple means to remove polystyrenes from the product.

The product/polystyrene ratio was increased from 1 : 40 to 1 : 5 (moles of **6** to moles of polystyrene  $\text{C}_6\text{H}_5$ ) by precipitation from the crude chloroform solution using methanol. However, the overall yield was disappointing; from three experiments on a similar scale the yield of crude product was only 8.8%, 6.9% and 8.3%. The silacyclopentane product could be purified by vacuum distillation, allowing a study by NMR spectroscopy and EIMS.

The  $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$  COSY NMR spectra, shown in Figures 3.2 and 3.3, were satisfactory for this product.



Figure 3.2  $^1\text{H}$  NMR Spectrum of 1-methyl-2,5-diphenylsilacyclopentane (**6**) diastereoisomer mixture.

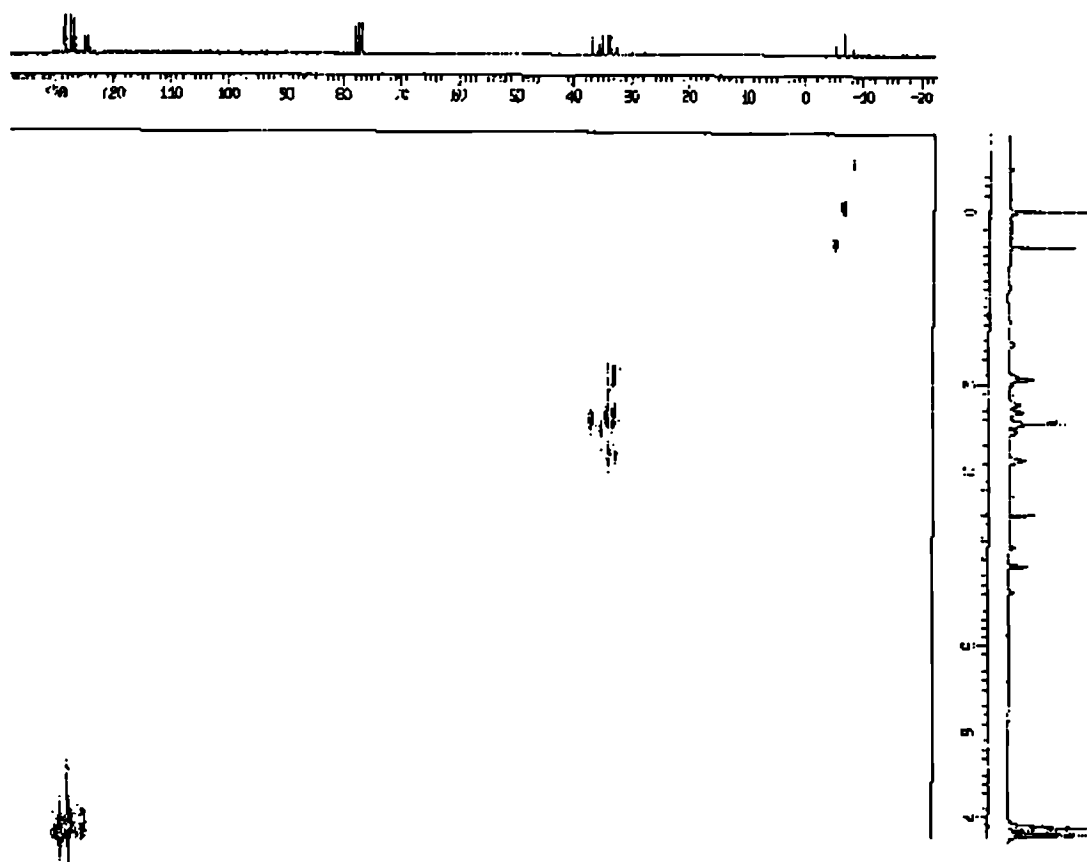


Figure 3.3  $^1\text{H}$ - $^{13}\text{C}$  COSY spectrum of 1-methyl-2,5-diphenylsilacyclopentane (**6**) diastereoisomer mixture.

The presence of isomers of **6** was apparent from both NMR spectra and from the GC/MS (Figure 3.4). The spectra of the isomers are discussed in detail later in this chapter.

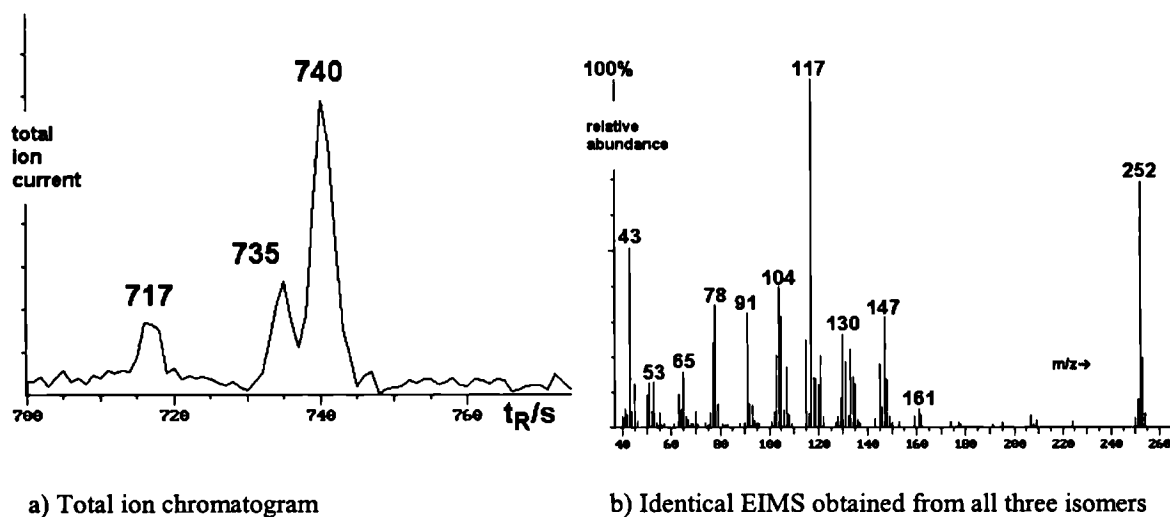


Figure 3.4 GC/MS of 1-methyl-2,5-diphenylsilacyclopentane (**6**) diastereoisomer mixture.

Distillation had no effect on the isomer ratio and was therefore not viable as a means of separating the unwanted *meso*-isomers from the racemic product. The SiCH<sub>3</sub> protons of the three isomers had chemical shifts of -0.51, -0.01 and 0.40 ppm. This was not unexpected and arises from the orientation of the methyl group with respect to the two phenyl groups, as discussed for compound 4.

NMR gave an indication of the level of polystyrene impurity in the fractions obtained by distillation at 0.08 mm Hg (Table 3.1).

Fraction	bp / °C	Yield / g	GC peak area <sup>1</sup>	SiCH <sub>3</sub> : ArH ratio <sup>2</sup>
1	85-110	0.55	3	3 : 16
2	110-115	1.2	3	3 : 15
3	115-120	0.8	5	3 : 11.3
4	120-125	0.55	3	3 : 8.7
5	125-135	0.3	1	nd
6	135-145	0.5	1	3 : 6.4

Notes

- 1 relative peak area of product isomers, same mass of sample injected
- 2 ratio of total SiCH<sub>3</sub> signal integral to aromatic proton integral (theoretical = 3:10)

Table 3.1 Analytical data on fractions of from distillation of 1-methyl-2,5-diphenylsilacyclopentane (6).

The fractions had a wide range of SiCH<sub>3</sub> : ArH ratios. The lower-boiling fractions had the lower ratio of SiCH<sub>3</sub> signals to aromatic signals. The excess aromatic signal was due to the presence of polystyrene oligomers. The SiCH<sub>3</sub> region still contained a number of small bands spread across the region, so that some of the excess aromatic signal may have been due to silicon containing copolymers of polystyrene. The presence of silicon-containing impurities was particularly evident in the final fraction, which had a high SiCH<sub>3</sub> : ArH ratio.

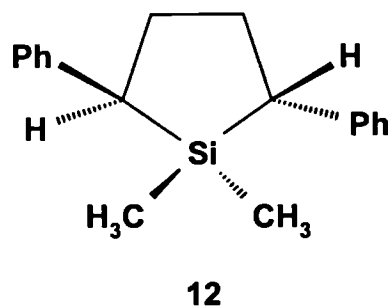
The fraction that had a ratio closest to that of the pure compound, 3:10, (fraction 3) also gave the largest GC response (GC peak area due to product per unit mass injected). The

total yield of distilled **6** was 3.9g (3.6% overall th.) and the yield of the most pure fraction (fraction 3) was 0.8g (0.7% overall th.)

The NMR data from the purified product were consistent with the compound having the expected structure, and being a mixture of the diastereoisomers shown in Scheme 3.1.

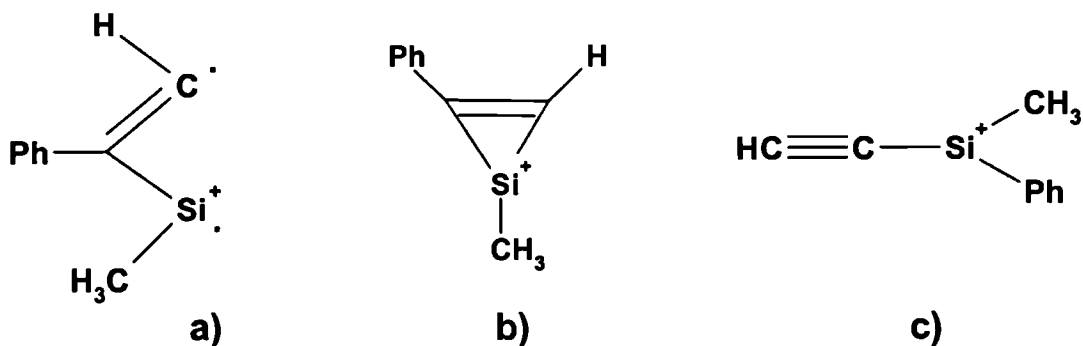
The EI mass spectrum was also satisfactory for the proposed structure.

There were many similarities with the EIMS of the 1,1-dimethyl analogue **12**, which was investigated by Maruca *et al.*<sup>167</sup>



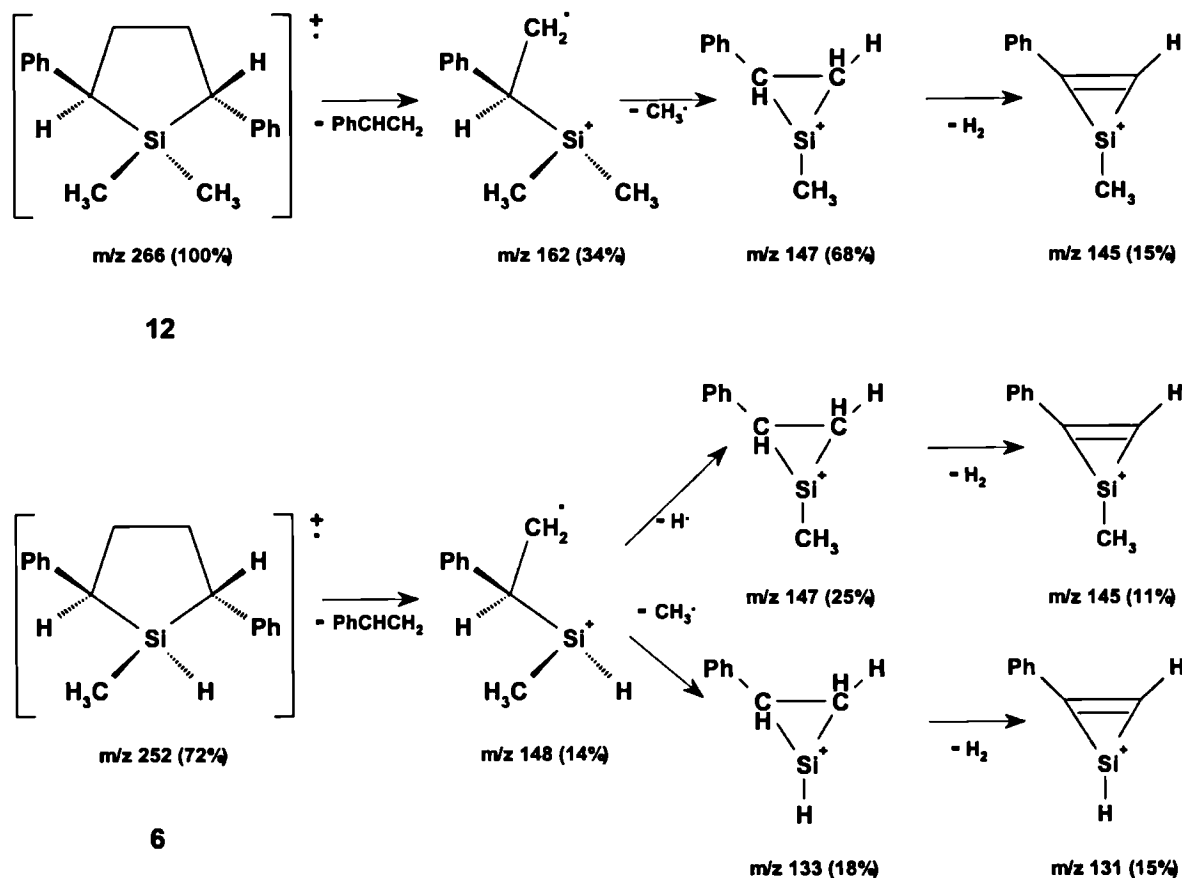
Maruca studied **12** and some related compounds (1,1-dimethyl-2,5-diphenyl-1-sila-2,4-cyclopentadiene, 1,1-dimethyl-2,3,4,5-tetraphenyl-1-sila-2,4-cyclopentadiene, 1,1,4,4-tetramethyl-2,3,5,6-tetraphenyl-1,4-disila-2,5-cyclohexadiene) and concluded that many of the more abundant ions appeared to contain silicon, some of which could only have arisen from rearrangements. In the spectrum of **12** they found that at least 16% of the ion current was carried by rearranged ions and they were able to identify likely migration processes which resulted in the formation of these rearranged ions.

The base peak of **6** was at  $m/z$  117, which was also a major ion in the spectrum of **12**. Maruca attributed this to  $[C_9H_9]^+$ , a daughter of the molecular ion, presumably  $[PhCHCHCH_2]^+$ . The molecular ion of **6** was the second-most abundant ion, as was the case for **12** reported by Maruca (although in the analysis of the sample of **12** reported here, it was the base peak). One of the three most abundant ions in the spectrum of **12**, having  $m/z$  147, had the formula  $C_9H_{11}Si$ . This was a daughter of the radical ion  $[C_{10}H_{14}Si]^{\bullet+}$  ( $m/z$  162). The ion with  $m/z$  147 was the parent of an ion with  $m/z$  145,  $[C_9H_9Si]^+$ , for which three possible structures were proposed, as shown in Scheme 3.3.



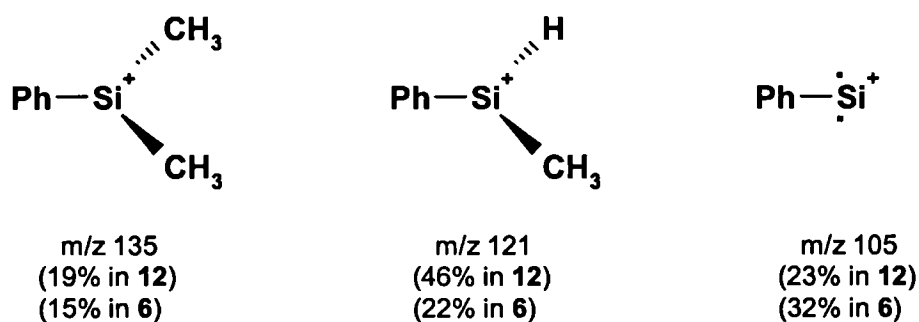
Scheme 3.3 Proposed structures for the ion with  $m/z$  145 (from reference 167)

Maruca pointed out that, although it requires some rearrangement, c) should still be considered because it would be the most stable structure, not having two unpaired electrons as in a) or a highly strained three-membered ring as in b). This ion was not among the eight most abundant ions in either **6** or **12**, but the parent ( $m/z$  147) was more significant in these compounds. In the EIMS of **6** the ion with  $m/z$  147 had a relative intensity of only one third its abundance in **12**. As can be seen from Scheme 3.4, one reason for this is that  $[M - 104]^{+·}$  has a choice of fragmentation pathways in the case of **6**, but not in **12**. In a study of some similar compounds,<sup>172</sup> cyclic species were among those proposed for the ion radical and ion with  $m/z$  162 and 147 in the EIMS of the 2,4-diphenyl analogue of **12**. Possible fragmentation pathways giving rise to some of the larger silicon-containing ions from silacyclopentanes **12** and **6** are shown in Scheme 3.4. Many of the ions are resonance stabilised. Ions with methyl groups bound to silicon were generally more abundant than their SiH counterparts.



Scheme 3.4 Possible fragmentation pathways giving rise to some of the larger silicon-containing ions from silacyclopentanes **12** and **6**.

Structures for the other major silicon-containing ions in the EIMS of **12** were proposed by Maruca and are shown in Scheme 3.5. These can only have been formed as a result of rearrangement.



Scheme 3.5 Proposed structures for the other major silicon-containing ions in the EIMS of **12** and **6**.

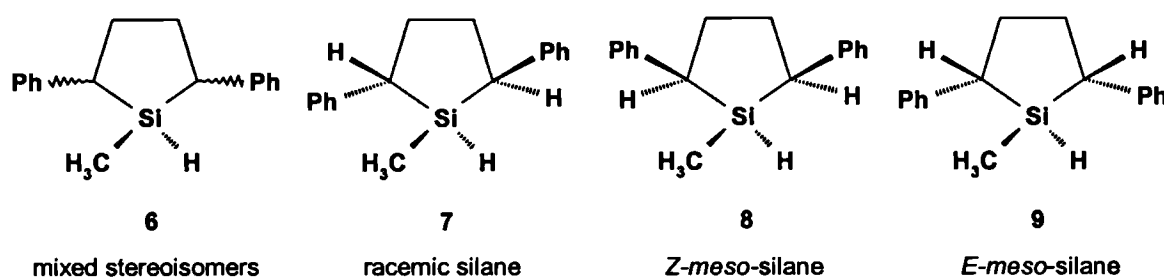
For each of the four compounds studied by Maruca, the ion with *m/z* 105 was assigned as the silicon-containing species shown in Scheme 3.5, rather than the stable alternative,



$[\text{PhCHCH}_3]^+$ . The parent ion ( $m/z$  131) was assigned the formula  $\text{C}_8\text{H}_7\text{Si}$ , rather than the alternative ( $\text{C}_{10}\text{H}_{11}$ ). Assuming that the ion at  $m/z$  131 was correctly assigned as being the parent, and that it had the structure shown in Scheme 3.4, it would seem unlikely to fragment to  $[\text{PhCHCH}_3]^+$ . On this basis it is believed that the fragment with  $m/z$  105 (32% RA) in **6** was also as shown in Scheme 3.5.

The product (**6**) was found to be contaminated with an impurity ( up to about 7% of the concentration of **6**, as determined by GC relative peak area). This was believed to be 1,4-diphenylbutane. The major ions in the EIMS were the molecular ion,  $m/z$  210 ( $\text{M}^+$ , 24%), and fragments  $[\text{C}_7\text{H}_8]^+$   $m/z$  92 (48%) and the tropylium ion  $m/z$  91 (100%).

### 3.1.2 Resolution of Diastereoisomers and Enantiomers of 1-Methyl-2,5-diphenylsilacyclopentane (**6**)



As noted in the introduction, Barrett *et al*<sup>159</sup> were unable to resolve the diastereoisomers of 1-allyl-2,5-diphenylsilacyclopentane by distillation or extensive chromatography. However, using HPLC (under normal phase achiral conditions) it was possible to resolve the diastereoisomers of 1-methyl-2,5-diphenylsilacyclopentane (**6**). This contrasted with the inability to resolve the isomers of the closely related silane **4** (Section 2.2), which was due, at least in part, to the poor retention of **4** when run under identical conditions to those successful with **6**.

At low HPLC loadings it was possible to obtain very pure samples of the racemic *E*-compound (**7**) and the two *meso*-isomers (**8** and **9**). Some of this purity was sacrificed as the HPLC loading was increased to obtain larger samples of each diastereoisomer for NMR analysis. In the case of **7**, a relatively large amount of silane was produced from which the chlorosilane, free of diastereoisomeric impurities could be generated. The *meso*-isomer that

was eluted first from the HPLC (8) was also eluted first from the GC. The major component of the mixture (7), which was the second-eluted isomer from the HPLC, eluted last from the GC (as expected, the racemate was the major component in all preparations). The last-eluted isomer from the HPLC (9) had intermediate retention on the GC.

At low HPLC loadings it was also possible to resolve the impurity suspected to be 1,4-diphenylbutane. Although no particular attempts were made to purify this component, fractions of 6 were obtained containing up to 46% 1,4-diphenylbutane (by GC peak area). As noted above, the identification of this compound was based on the EIMS. NMR of the enriched sample supported the conclusion that this compound was 1,4-diphenylbutane.

Having separated out the *meso*-isomers, various HPLC phases were employed in an attempt to resolve the enantiomers. Cellulose triacetate and ChiralPak AD (amylose tris(3,5-dimethylphenylcarbamate) coated on 5  $\mu$ m spherical silica) were unable to effect the resolution. However, the cellulose equivalent of the latter phase, Chiralcel OD, (cellulose tris(3,5-dimethylphenylcarbamate) coated on 5  $\mu$ m spherical silica) provided an excellent separation ( $\alpha = 1.40$ ,  $R_s = 3.46$ ).

Small-scale preparative chiral HPLC under these conditions provided good samples of the resolved enantiomers. The GC separation of diastereoisomers, the achiral HPLC separation of diastereoisomers and the chiral HPLC separation of enantiomers is shown in Figure 3.5.

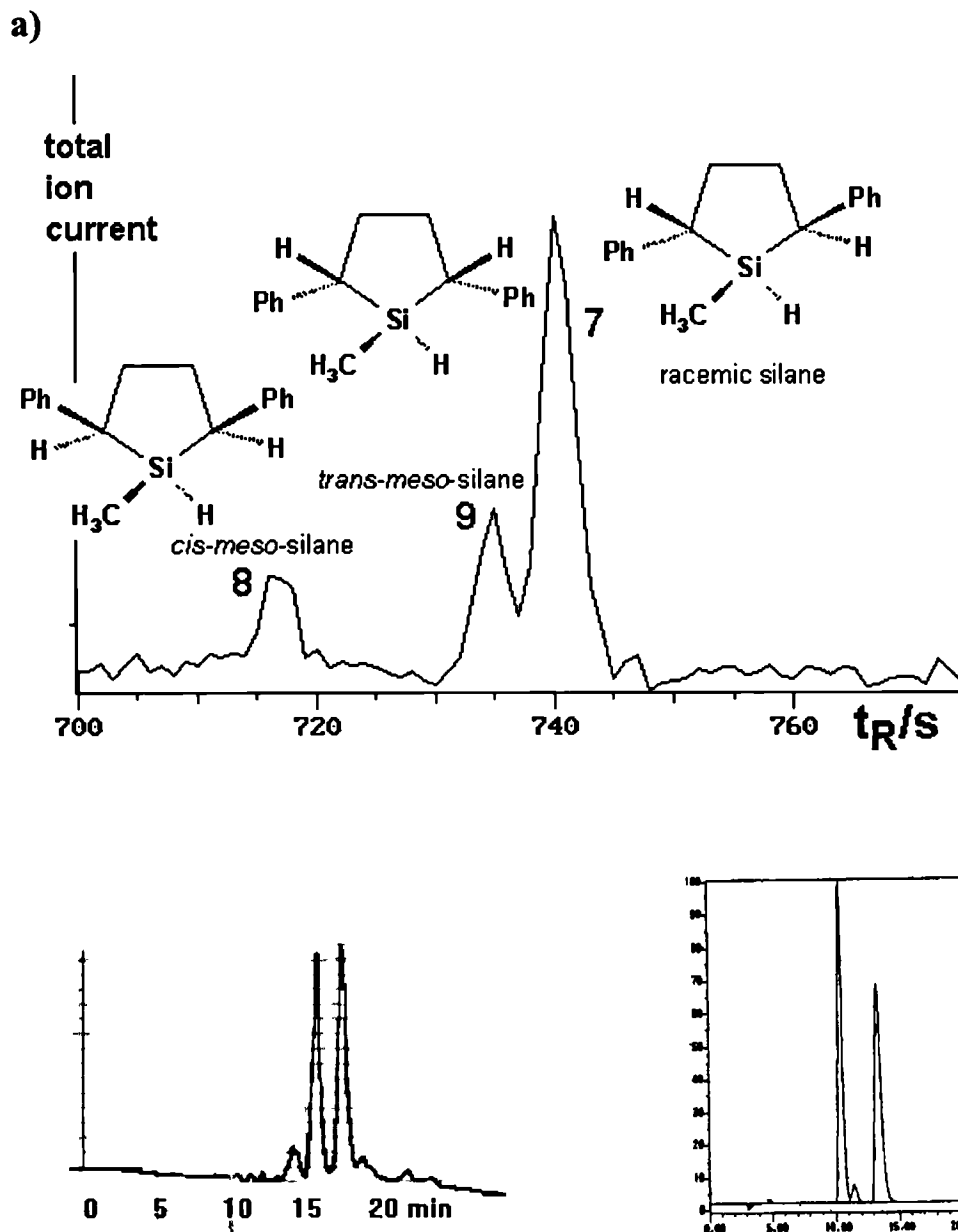
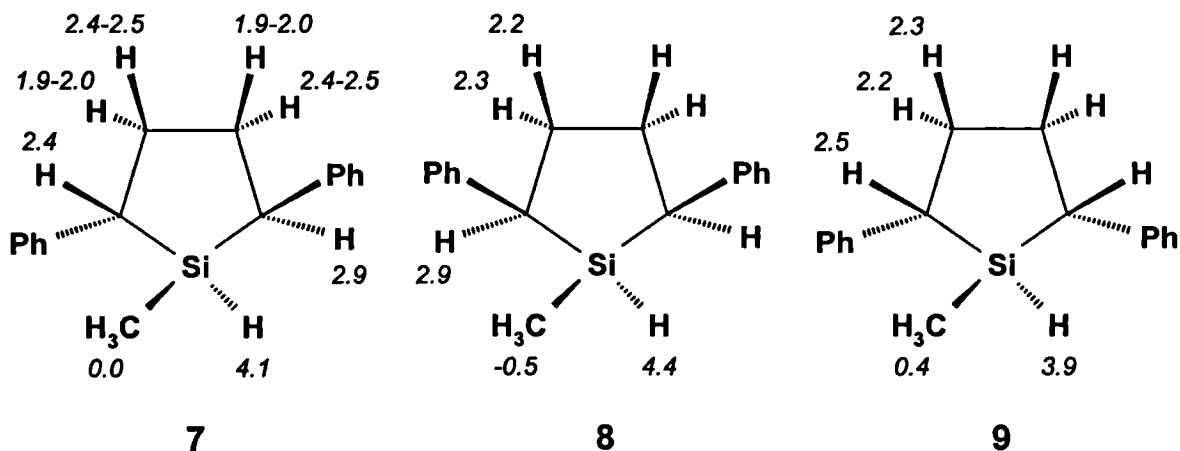


Figure 3.5 Summary of the chromatographic separations of the stereoisomers of 1-methyl-2,5-diphenylsilacyclopentane (6)

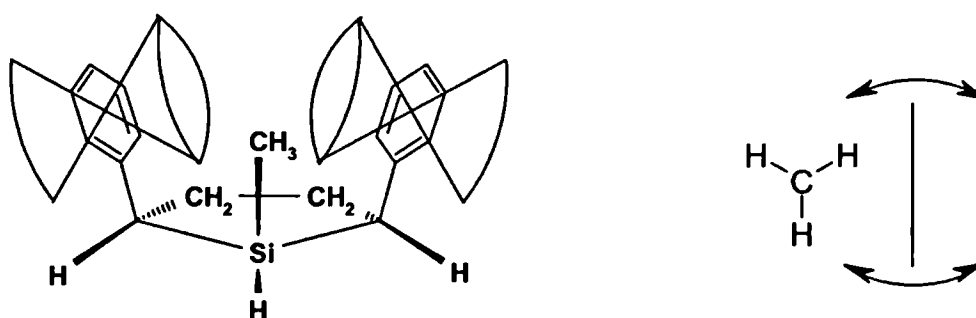
- a) GC separation of diastereoisomers  
 b) Achiral HPLC separation of diastereoisomers    c) Chiral separation of enantiomers

### 3.1.3 Characterisation of Diastereoisomers and Enantiomers of 1-Methyl-2,5-diphenylsilacyclopentane (6)

The NMR spectra of the first and third eluted isomers from the HPLC represented more symmetrical structures, *i.e.* they were the *meso*-isomers. The <sup>1</sup>H NMR signals were assigned to the three isomers (Scheme 3.6) on the basis of magnetic shielding considerations, exemplified for the *Z-meso*-isomer (8) in Scheme 3.7.



Scheme 3.6  $^1\text{H}$  NMR Assignments for the resolved diastereoisomers of **6**



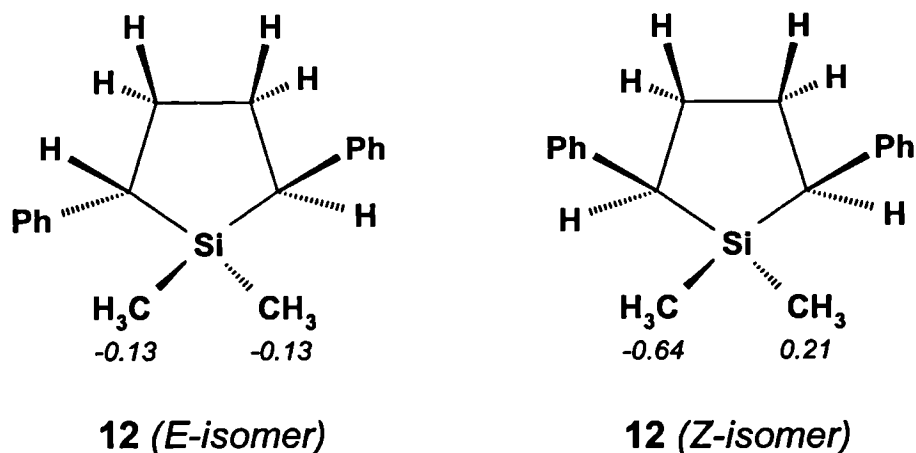
a) The shielding cones of the phenyl rings

b) The limited rotational freedom of the plane of the phenyl ring

Scheme 3.7 Nuclear magnetic shielding of the  $\text{SiCH}_3$  group in the *Z*-*meso*-isomer (**8**)

The plane shown in **b** represents the plane of the phenyl ring, as seen from above in diagram **a**

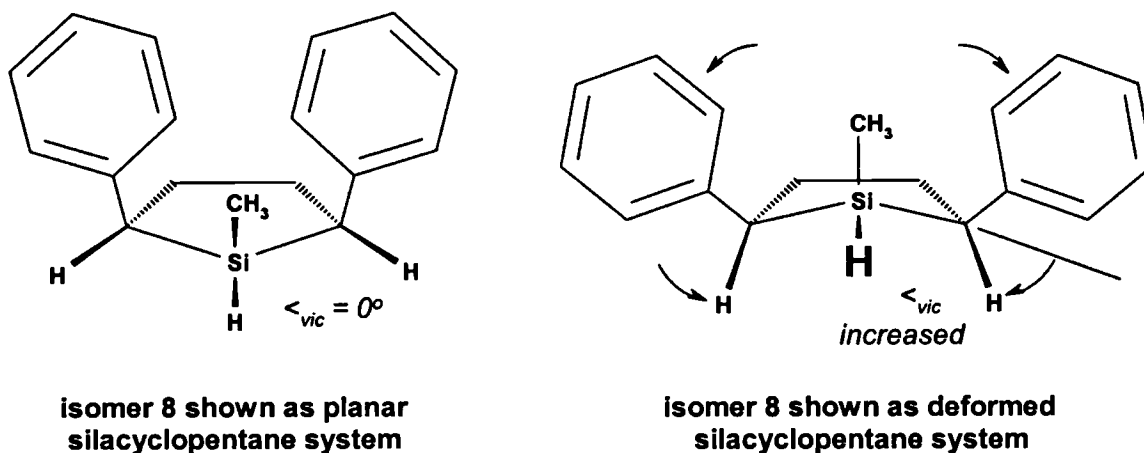
The intermediate chemical shift ( $\delta_{\text{H}} -0.5$ ) was due to the enantiomers. The relatively high methyl shift (0.40 ppm) in the *E*-*meso*-isomer (**9**) showed that, despite the distance between the phenyl ring and the  $\text{SiCH}_3$  group, there was a considerable deshielding effect in this isomer. These values are comparable with the shifts reported and the assignments made by Gilman<sup>173</sup> for the silicon-methyl groups of 1,1-dimethyl-2,5-diphenylsilacyclopentane (**12**) (*i.e.* the homotopic silicon-methyl groups of the *E*-isomers at -0.13 ppm, and the diastereotopic silicon-methyl groups of the *Z*-isomer at -0.64 and 0.21, (solvent =  $\text{CCl}_4$ ), as shown in Scheme 3.8).



Scheme 3.8 Proton chemical shifts for the SiCH<sub>3</sub> groups of the two diastereoisomers of **12**, reported by Gilman.<sup>173</sup>

The other <sup>1</sup>H shifts of **7**, **8** and **9** are consistent with the assignment shown in Scheme 3.6. The SiH was less shielded in the *Z*-meso-isomer (**8**) than in the *E*-meso-isomer (**9**), the enantiomers (**7**) being intermediate. The benzylic proton of **8** (2.9 ppm) was deshielded relative to that of **9** (2.5 ppm). This may have been due to the preferred orientation of the phenyl ring; rotation about the C-phenyl bond being hindered by the SiCH<sub>3</sub> group. This hindrance would not occur in **9**. Alternatively, this proton could have been shielded by the SiCH<sub>3</sub> group in **9**. Either of these proposals, or a combination of the two effects, would account for the difference in chemical shift between the benzylic protons of **8** and those of **9**. Considering the CH<sub>2</sub> protons in **8** and **9**, it is clear that the shielding effect of the phenyl ring is very similar (all four CH<sub>2</sub> protons have δ<sub>H</sub> = 2.2 or 2.3). By examination of models, it appears that, relative to the shielding cone of the phenyl ring, the benzylic protons are in a fairly similar environment to the CH<sub>2</sub> protons in **8** and **9**. This suggests that there is also little difference between the phenyl ring shielding of the benzylic protons of **8** and **9**. On that basis, it appears that the difference in chemical shift between the benzylic protons of **8** and those of **9** is due to the difference in shielding by the SiCH<sub>3</sub> group. The multiplicity of the signals in the <sup>1</sup>H NMR spectrum was as expected for the given assignments. The <sup>1</sup>H-<sup>1</sup>H COSY NMR spectra of all isomers confirmed that the SiH protons were coupled to the SiCH<sub>3</sub> protons, as expected. Other proton couplings were confirmed, including that of the SiH proton to the vicinal benzylic proton in the *E*-meso-isomer (**9**), but not in the *Z*-meso-isomer (**8**). This can be rationalised by considering the ring

deformation that arises from steric interaction between the two phenyl and the methyl groups. This interaction is shown in Scheme 3.9 for the *Z-meso*- isomer (**8**). The effect on the vicinal bond angle can be predicted and thus the proton-proton coupling estimated from the Karplus equation.<sup>174</sup> In the *Z-meso*- isomer (**8**) the vicinal bond angle would be 0° if the ring were planar, but would increase to relieve the steric interaction between the phenyl and methyl groups as shown in Scheme 3.9. As the angle approached 90°, coupling would reduce to zero, which would explain the lack of observed coupling in this isomer.



Scheme 3.9 The effect of ring deformation arising from phenyl-methyl-phenyl steric interaction on the angle between the vicinal bonds to SiH and benzylic protons

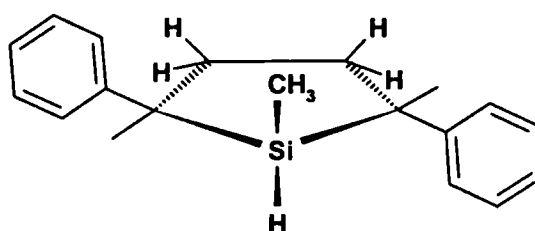
In the *E-meso*-isomer (**9**) the vicinal bond angle would be 120° if the ring were planar. According to the Karplus equation, coupling between the vicinal protons is expected. However, this angle will increase so as to reduce the steric interaction between the phenyl groups in the same way as shown for **8** in Scheme 3.9. As the vicinal bond angle approached 180°, so the coupling would increase. This is in accordance with the observed coupling in **9**. As with the <sup>1</sup>H NMR spectrum, the <sup>13</sup>C NMR of **9** showed it to have a symmetric structure. The DEPT spectrum of **9** confirmed the assignment of the two <sup>13</sup>C signals to the four carbon atoms of the silacyclopentane ring. The <sup>13</sup>C-<sup>1</sup>H COSY spectrum of **9** was entirely consistent with the proton assignments given in Scheme 3.6.

The simplification of the NMR spectra of the two *meso*- isomers assisted in the interpretation of the spectra of the enantiomers.

### NMR of racemic 7.

The  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra, and the  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$  COSY NMR spectra of this fraction were studied in detail. None of the protons attached to the ring are magnetically equivalent. Because of this, it was not possible to measure coupling constants where protons with similar shifts were coupled to two or more other protons. COSY spectra provided useful coupling evidence in such cases.

The proton spectrum assignments are noted above in Scheme 3.6. Comparisons of the proton spectrum of 7 with those of the *meso*-isomers 8 and 9 were very useful. Whereas the *meso*-isomers were expected to have deformed silacyclopentane rings, the enantiomers were expected to be more planar, making some of the assignments easier. The two diastereotopic benzylic protons of 7 had very similar shifts (2.4 and 2.9 ppm) to those of the two *meso*-isomers (2.5 and 2.9 ppm). Although the benzylic proton signal at 2.4 ppm was coincident with two  $\text{CH}_2$  signals, the assignment was confirmed by its coupling to the SiH proton. The SiH proton was also coupled to the other benzylic proton (at 2.9 ppm) in contrast to the analogous *meso*-isomer where the lack of coupling was attributed to ring deformation. The shifts of the  $\text{CH}_2$  protons were less similar in the racemate than in the *meso*-isomers. The reason for this is that the silacyclopentane ring of the racemate is expected to be approximately planar, so that one of the two protons of each  $\text{CH}_2$  group is eclipsed by the adjacent phenyl ring, as shown in Scheme 3.10. The phenyl ring will therefore more effectively shield this proton compared with its geminal partner.



Scheme 3.10 The approximately planar silacyclopentane ring of the racemate 7. The proton of each  $\text{CH}_2$  group that is on the same face of the silacyclopentane ring as the phenyl group will experience greater shielding than that which is on the opposite face.

These considerations are incorporated in the complete proton spectrum assignment shown in Scheme 3.6. It is expected that there will be some ring deformation arising from the interaction of the silicon methyl group and the adjacent phenyl group. However, this did not create a large difference between the CH<sub>2</sub> protons in similar environments (*i.e.* those positioned *E*- to each other).

All the <sup>13</sup>C signals were resolved (without distinguishing all the signals from the two phenyl groups). The DEPT spectrum showed the two CH(Ph) atoms to have a  $\delta_C$  of 33.68 and 36.73 ppm, and the two CH<sub>2</sub> atoms at a  $\delta_C$  of 32.89 and 33.88 ppm. From the <sup>13</sup>C-<sup>1</sup>H COSY spectrum, the benzylic protons with a  $\delta_H$  of 2.9 and 2.4 ppm were attached to the CH(Ph) carbon atoms having a  $\delta_C$  of 33.68 and 36.73 ppm respectively; the four protons with a  $\delta_H$  of 2.4 and 1.9 ppm were attached to the carbon atoms having a  $\delta_C$  of 32.89 and 33.88 ppm. These data confirmed the assignments of the CH<sub>2</sub> protons and the fact that, although diastereotopic, the *E*-vicinal protons were unresolved.

*NMR in the assignment of configuration to the three diastereoisomers of the cyclic silanes (7, 8 and 9) and the acyclic analogues (diastereoisomers of 4)*

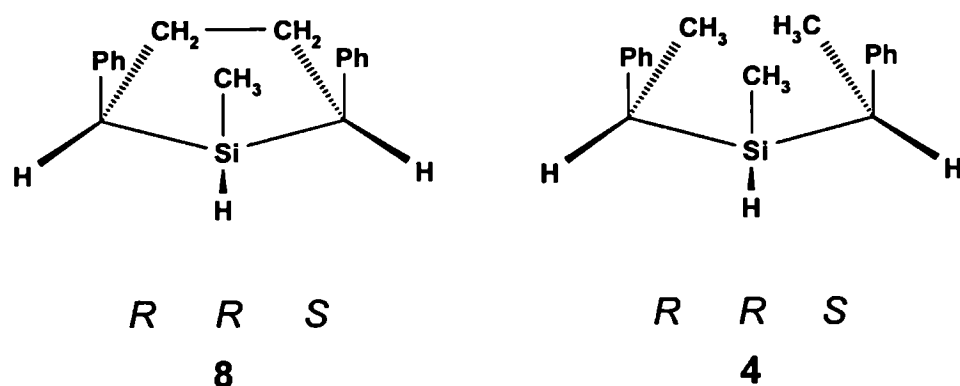
The protons of the SiCH<sub>3</sub> group were shielded in the *Z*-*meso*-isomer (**8**, which had the 1*R*,2*R*,5*S* configuration), deshielded in the *E*-*meso*-isomer (**9**, 1*S*,2*R*,5*S*), and intermediate in the enantiomers (**6**, 1*R*,2*R*,5*R*, and 1*S*,2*S*,5*S*). This was not surprising; a simple model (Scheme 3.7) shows how the restriction of conformation of the C-C-Si-C-C backbone and the limited rotational freedom of the phenyl ring produces a shielding cone which can influence both the carbon nucleus and the protons in **8**. On the other hand, the phenyl ring in **9** has complete rotational freedom which results in overall deshielding of the carbon nucleus and the protons of the SiCH<sub>3</sub> group which explains the observed lower chemical shifts of both nuclei. It is interesting to compare these NMR results with those obtained from the three diastereoisomers of the analogous compound **4**.

Whereas the difference between the SiCH<sub>3</sub> proton chemical shifts of the *meso*-isomers **8** and **9** was large ( $\Delta\delta_H = 0.91$  ppm), that of the equivalent diastereoisomers of the two *meso*-isomers of **4** was relatively small ( $\Delta\delta_H = 0.30$  ppm). This was related to the conformational



rigidity of the cyclic system (**8** and **9**) compared with the less constrained acyclic analogue (**4**). However, despite the conformational freedom of **4**, there was still a considerable difference between the SiCH<sub>3</sub> proton chemical shifts of the *meso*-isomers.

Because **4** is acyclic, it is not possible to refer to its diastereoisomers as being *Z*- or *E*-. The similarity of the diastereoisomers of **4** and **7**, **8** and **9** means that it is convenient to relate them in terms of absolute configuration, but unfortunately the numbering system is different. To overcome this, and for the purposes of this part of the discussion only, the two compounds are described by the absolute configuration at each centre, in the order C-Si-C. Two configurationally related diastereoisomers of the cyclic and acyclic silanes are compared in Scheme 3.11.



Scheme 3.11 Comparison of two structurally related diastereoisomers of the cyclic and acyclic silanes **8** and **4**.

The isomer of the cyclic silane having the most-shielded SiCH<sub>3</sub> protons (*i.e.* the *RRS Z-meso*-isomer, **8**) clearly had *RRS* relative configuration. However, the diastereoisomer of the acyclic analogue with the same relative configuration (*RRS-4*), was believed to be the diastereoisomer with the least shielded SiCH<sub>3</sub> group. This assignment was tentatively made in Section 2.2 and is now confirmed. The particular conformation of *RRS-4* shown in Scheme 3.11 is the one most closely related to that of **8**, and would lead to maximal SiCH<sub>3</sub> proton shielding. However, this conformation would be disfavoured by the large steric interaction between the two CCH<sub>3</sub> groups. Even a small angular displacement from this conformational extreme leads to loss of shielding as the shielding cone of the phenyl ring moves away from the SiCH<sub>3</sub> group. This is not the case with the other *meso*-

diastereoisomer of **4** (the *RSS*-diastereoisomer), which can attain a conformation where the SiCH<sub>3</sub> protons experience maximal shielding (as shown for *RRS-4* in Scheme 3.11), without steric interaction between the two CCH<sub>3</sub> groups.

*Comparison of <sup>13</sup>C-<sup>1</sup>H COSY spectra of the three diastereoisomers of the cyclic silanes (7, 8 and 9) and the acyclic analogues (diastereoisomers of 4)*

The <sup>13</sup>C-<sup>1</sup>H correlation spectra of a typical product mixture containing **7**, **8** and **9** (Table 3.2) showed that not only the protons but also the carbon nucleus of the SiCH<sub>3</sub> were shielded in the *Z-meso*-isomer (**8**), deshielded in the *E-meso*-isomer (**9**), and intermediate in the enantiomers (**7**). This showed that the phenyl ring produced a shielding cone which influenced both the carbon nucleus and the protons in **8**, and likewise a deshielding effect over both nuclei in **9**. However, it is interesting to compare the opposite finding in the related compound **4** (Table 3.2). The diastereoisomer which had the most-shielded protons of the SiCH<sub>3</sub> group had the least-shielded carbon nuclei. One explanation of this might be associated with the range over which the shielding cone can shield the SiCH<sub>3</sub> protons and carbon nuclei simultaneously. In the constrained structure, **8**, the phenyl ring shielded both the carbon and hydrogen nuclei. The conformational extreme shown in Scheme 3.7a resulted in maximal carbon and hydrogen shielding. Deviation from this extreme leads to a greater loss of shielding of the carbon nucleus compared with that of the proton. In both acyclic *meso*-structures, a far wider range of conformations are possible. In some of these conformations both nuclei are shielded, in other conformations both nuclei are deshielded, while in intermediate conformations it is possible for the shielding cone to bisect the C-H bond, resulting in proton shielding but carbon nucleus deshielding. If, on average, one diastereoisomer of **4** existed in such an intermediate conformation, then it is possible for the observed inverse correlation of proton and carbon nucleus to occur.

Overall, the assignments for the SiCH<sub>3</sub> group of the three diastereoisomers of the cyclic silanes (**7**, **8** and **9**) and the acyclic diastereoisomers of **4** were as shown in Table 3.2.

	cyclic silanes			acyclic silanes		
$\delta_{\text{H}}$	+0.40	-0.01	-0.51	+0.04	-0.14	-0.26
$\delta_{\text{C}}$	-5.33	-6.81	-8.66	-10.08	-9.73	-9.20
proposed configuration	<i>RSS</i> (9)	<i>RRR</i> (7) <i>SSS</i>	<i>RRS</i> (8)	<i>RRS-4</i>	<i>RRR-4</i> <i>SSS-4</i>	<i>RSS-4</i>

Table 3.2 Proton and carbon chemical shifts for the SiCH<sub>3</sub> group in the resolved diastereoisomers of the cyclic silane **6** (*i.e.* **7**, **8** and **9**) compared with those of the acyclic silane **4**; with their proposed configurations.

*CD spectra of the resolved enantiomers of 7*

As expected, the NMR spectra of the resolved enantiomers were identical, as were the GC/MS chromatograms and EIMS. Circular dichroism spectroscopy gave particularly useful information about the two enantiomers. The relatively weak absorption band at *ca.* 230 nm was associated with a strong CD band, which was of approximately equal magnitude (equal molar CD,  $\Delta\epsilon$ ) and of opposite sign for the two enantiomers. The CD spectrum from both enantiomers is shown, in molar terms, in Figure 3.6. The lower spectrum shows slight differences between the UV absorbance of the two samples; this is because they were recorded at slightly different concentrations. A measure of enantiomeric purity, the anisotropy factor, defined as  $g = \Delta\epsilon / \epsilon^{175}$  is a parameter which is particularly useful because the CD spectrometer measures the two components simultaneously. This obviates the need for accurately weighing extremely small samples and allows the on-line acquisition of enantiomeric purity data from liquid chromatography (*i.e.* using a flow cell). However, in this work, all such spectroscopic analyses were performed off-line.

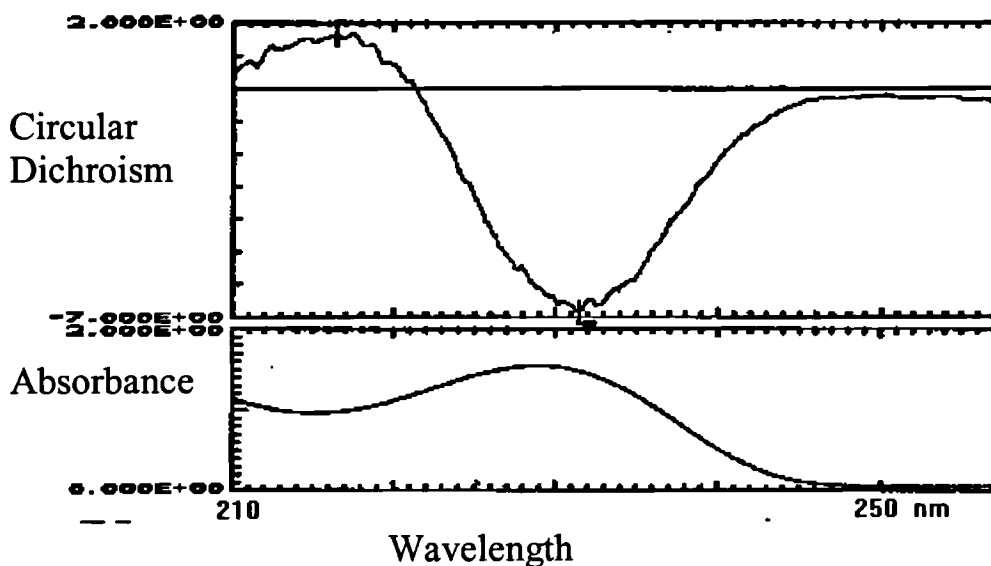


Figure 3.6 Circular dichroism and UV spectra of one resolved enantiomer of **7**

For the first-eluted enantiomer the value of the molar CD was  $\Delta\epsilon_{231} = +7.5 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ . The molar absorptivity was  $\epsilon_{231} = 20400$ .

The anisotropy factor was therefore  $g_{231} = \Delta\epsilon_{231} / \epsilon_{231} = +3.70 \times 10^{-4}$ .

For the second-eluted enantiomer the value of the molar CD was  $\Delta\epsilon_{231} = -6.9 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ . The molar absorptivity was  $\epsilon_{231} = 20800$ .

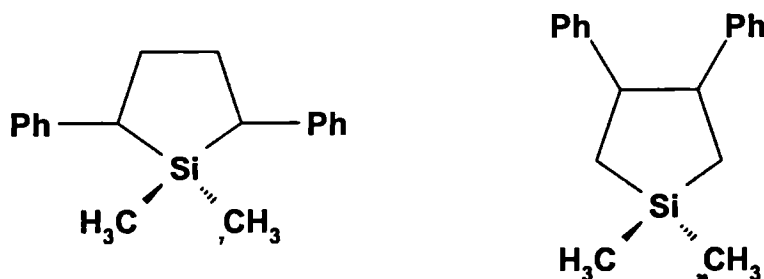
The anisotropy factor was therefore  $g_{231} = \Delta\epsilon_{231} / \epsilon_{231} = -3.3 \times 10^{-4}$ .

The first-eluted fraction had a lower absorptivity ( $\times 0.98$ ) because it was 'chemically less pure', *i.e.* it had a lower concentration of compound **7**. However, the first-eluted fraction had a higher ( $\times 1.09$ ) CD. It therefore had a higher enantiomeric purity. These two figures are combined in the anisotropy factor,  $g$ , which gives a value for the enantiomeric purity, corrected for the presence of chemical impurities. Thus the ratio of the anisotropy factors of the two samples ( $\times 1.11$ ) showed that the enantiomeric purity of the first-eluted enantiomer was  $1.11 \times$  greater than that of the second-eluted enantiomer.

These data were used as the basis for stereochemical comparisons and were used to compare data from some of the diastereoisomers containing similar chromophores.

### 3.1.4 Variation of Reaction Conditions in an Attempt to Improve the Yield of 1-Methyl-2,5-Diphenylsilacyclopentane (6)

Examination of the literature revealed that investigators of this reaction, using the *dimethylsilane*, experienced mixed success. Nefedov<sup>153, 154</sup> reported a yield of 30-50% of a mixture of isomers including **12** and the 3,4-diphenyl- substituted analogue (Scheme 3.12).



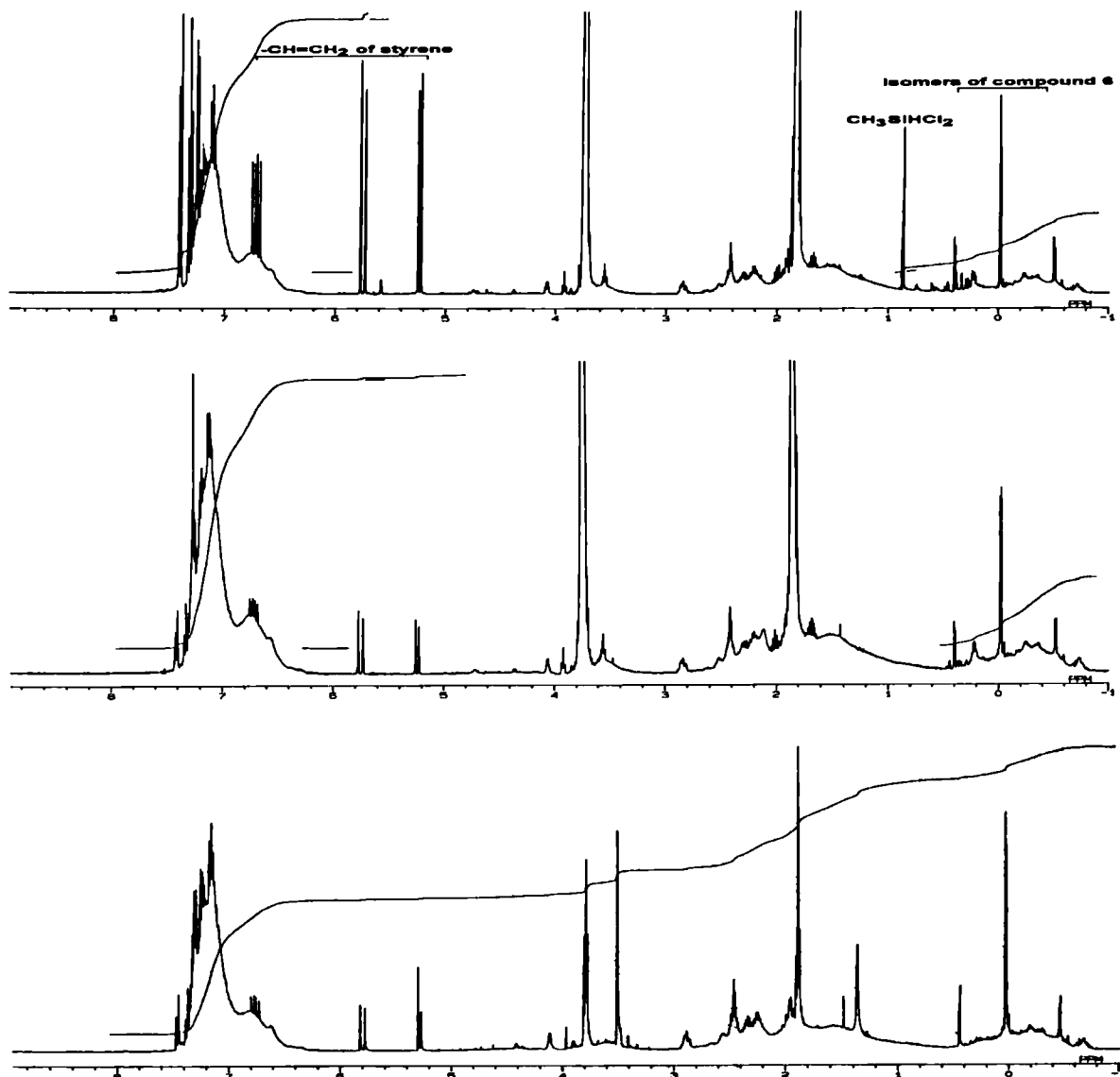
Scheme 3.12 1,1-dimethyl-2,5-diphenylsilacyclopentane (**12**) and the 3,4-diphenyl- analogue

By adding THF solutions of styrene and dichlorodimethylsilane to lithium, Weyenberg<sup>155</sup> obtained a 71% yield of the 2,5-diphenyl substituted isomers. However, when he altered the styrene/dichlorodimethylsilane molar ratio from 2:1 to 1:1, he obtained a 10% yield of the 3,4- disubstituted product, but no **12**. In the preparation described here, styrene was added to a dichloromethylsilane/lithium mixture in THF, so that there was always a deficiency of styrene. According to Weyenberg's work, this would be likely to reduce the yield of **6**. Although both authors used the *dimethyl* silane, it seemed likely that a change in the order of addition may improve the yield.

Although the product purification was difficult, <sup>1</sup>H NMR of the crude reaction product provided adequate evidence that the low yield of **6** was due to an inherent poor reaction yield rather than to losses in the work-up. <sup>1</sup>H NMR of the crude reaction product also gave a clear indication of any residual styrene or chlorosilane. The isomers of **6** were easily identified and the majority of the contribution to the integral over the SiCH<sub>3</sub> region appeared to be due to a range of signals from polymeric products containing SiCH<sub>3</sub> groups.

NMR was used in this way as the best means to determine the reaction yield as the preparation was varied (order of addition of reagents, ratio of reagents, temperature, type of

alkali metal) and in most cases the product was not worked up further. An example of the reaction monitoring by NMR is shown in Scheme 3.13. In this case the reaction was carried out on a 0.25 molar scale, with both the styrene and dichloromethylsilane being mixed together and added to sodium spheres in THF over a period of one hour, with the flask temperature being maintained below  $-60^{\circ}\text{C}$



Scheme 3.13      Typical NMR monitoring of the reaction to produce 1-methyl-2,5-diphenylsilacyclopentane (6)

Note that the reagents and products were easily identified as shown in the top spectrum. The bands at 1.8 and 3.7 ppm were due to residual THF. Top spectrum: Reaction mixture after 20 hours. Middle spectrum: Reaction mixture after 3 days. Lower spectrum: Reaction mixture after  $\text{CH}_2\text{Cl}_2$  / methanol precipitation. Note the improvement in the  $\text{SiCH}_3$  region.

Experiments to improve the yield of **6** are summarised in Table 3.3. The example shown in Scheme 3.13 is represented in the table as experiment 20. Unless noted otherwise, the conditions were essentially as recorded in Section 3.1.1.

Expt	Equivalents of reagents		Scale (mol)	Metal	Temp <sup>1</sup>	Conditions	Yield <sup>2</sup>
	Styrene	CH <sub>3</sub> SiHCl <sub>2</sub>					
1	1	1	0.144	Li <sup>3</sup>	0°C	Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 40 min	8.8%
2	1	1.2	0.144	Li	0°C	Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 30 min	6.9%
3	1	2	0.144	Li	<10°C	Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 5 min	8.3%
4	1	1	0.144	Li	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 80 min	15%
5	1.4	1	0.1	Li	<10°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 5 hours	13%
6	1	1	0.05	Li	<10°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 50 min	6%
7	1	1	0.05	Li	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 90 min	6%
8	1	1	0.05	Li	<-60°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 2 hours	6%
9	1	1	0.05	Li	<-60°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 1 hour. Fresh lithium used	6%
10	1	1	0.05	Li	<10°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 1 hour. Fresh lithium with high sodium content used	5%
11	1	1	0.05	K	<15°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 1 hour. Fresh potassium wire used	~0%
12	1	1	0.05	K	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 90 min	~2%
13	1	1	0.05	Na wire	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 60 min to freshly pressed sodium wire	15%
14	1	1	0.05	Na wire	<-60°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 60 min. After addition, stirred at 8°C for 16hr	8%

Expt	Equivalents of reagents		Scale	Metal	Temp <sup>1</sup>	Conditions	Yield <sup>2</sup>
	Styrene	CH <sub>3</sub> SiHCl <sub>2</sub>	(mol)				
15	1	1	0.05	Na wire	<-60°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 60 min. After addition, stirred at 8°C for 16hr	<3%
16	1	1	0.05	Na	<-60°C	THF better dried (over LiAlH <sub>4</sub> ). Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> and Na (spheres) over 30 min	10%
17	1	1	0.05	Na	20°C then reflux	THF ex-LiAlH <sub>4</sub> . Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 30 min with no temp control. After further 40 min, mixture refluxed	8%
18	1	1	0.05	Na	<10°C	'Anhydrous' THF ex-Aldrich Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 10 min	7%
19	1	1	0.05	Na	<-70°C	'Anhydrous' THF ex-Aldrich Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 120 min	13%
20	1	1	0.25	Na	<-60°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 70 min	8%
21	1	1	1.0	Na	<-50°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 45 min. After 48h, most residual sodium was fused together in one lump 0.6equiv. sodium remained	7% 0% <sup>4</sup>
22	1	1	1.0	Na 0.6 eq	<-25°C	As expt. 21, but deficit of sodium. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 3 h. After 44h, a total of 1.4l of methanol (no CH <sub>2</sub> Cl <sub>2</sub> ) added in portions to precipitate polymeric material	8%
23	1	1	1.0	Na 0.7 eq	<-50°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 60 min	8%
24	1	1	1.0	Na 0.66eq	0-5°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 2.5 hours	8%

Table 3.3 Summary of experiments to improve the yield of 6.

- Notes:
1. Temperature controlled during addition of reagent
  2. Yield of isolated *crude* product or, in cases where product not worked up, yield based on NMR spectrum of crude product (from ratio of integrals of product SiCH<sub>3</sub> signals to total SiCH<sub>3</sub> signals)
  3. Lithium was in the form of shot, unless noted otherwise.
  4. After CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> extractions. See text below.



*Observations on some of the above reactions.*

It was common for reaction mixtures to contain small amounts of residual reagents, including the alkali metal. It was particularly apparent in experiment 11 in Table 3.3 that, despite being used in stoichiometric proportion, there was a considerable amount of potassium remaining at the end of the reaction. In that case compound **6** was not apparent and the major products were polystyrene, residual  $\text{CH}_3\text{SiHCl}_2$  and polymers containing  $\text{SiCH}_3$  groups. In experiment 12, where styrene and  $\text{CH}_3\text{SiHCl}_2$  were added together, the reaction was slow, with some of all reagents remaining after 19 hours.

In experiment 17 the yield was not increased by refluxing the reaction mixture. In experiment 19 no product was apparent after the addition of reagents at low temperature. After stirring overnight at *ca.* 20°C, no chloromethylsilane remained, little styrene and some sodium was present.

Apart from the reactions using potassium, where very little product was obtained, it was difficult to select a procedure that reliably gave a significantly improved yield. Results were inherently variable for a number of reasons, including the variability of reaction conditions and the imprecision of the sampling and analysis. However, the approach taken in estimating the yield by analysing samples of the final reaction mixture did avoid the variability that arose in the work-up. The conditions used in experiment 13 gave the best yield of **6** while utilising fairly convenient conditions; these conditions were adopted for the later experiments (20-24) which were aimed at increasing the scale of reaction. In all these experiments the reaction flask was heated to glowing to drive off moisture. A mixture of styrene and  $\text{CH}_3\text{SiHCl}_2$  was added to sodium in 'anhydrous' THF (ex-Aldrich). After stirring overnight, the reaction mixture was typically a blue-grey colour, with small amounts of sodium apparent. In experiment 21 and in all the previous experiments, one equivalent of sodium, or a slight excess, was used. In experiment 21, one lump of sodium was removed, but it was difficult to remove all the residual sodium. During the work-up with methanol/dichloromethane there was considerable effervescence, which may have been due to the reactive by-products, or to the remaining flecks of sodium. The extracts contained approximately 0% product.

The presence of residual metal at the end of the reaction was presumed to be a result of the undesired polymerisation of styrene. To avoid problems in the work-up, later larger-scale experiments used a deficiency of sodium (0.6, 0.66 and 0.7 equivalents in experiment 22, 23 and 24 respectively). The sodium used in these experiments was in the form of chunks (*ca.* 0.5 cm). Also, it became increasingly more difficult to stir large volumes of reaction mixture using a magnetic stirrer, particularly as the viscosity increased with polymer production. Therefore, experiments at the 1.0 molar scale used an overhead paddle stirrer.

In experiment 22, using 0.6 equivalents of sodium, there appeared to be no sodium remaining after 44 hours stirring at 18°C. There was a small amount of styrene and dichloromethylsilane remaining, according to the NMR. Methanol was added to precipitate polymer, causing brief effervescence due to reaction with residual dichloromethylsilane. A total of 1.4 litres of methanol was added to the stirred mixture. In this case, no chlorinated solvent was added and the methanolic extracts were evaporated to give 32% crude product which was vacuum-distilled to yield four fractions. The isomer ratio of these fractions (from NMR integrals) is shown in Table 3.4, which shows that distillation was of limited use for purification of the enantiomer.

Fraction	bp / °C at 0.35mm Hg	Yield / % (% of overall theoretical yield)	Isomer ratio from NMR data		
			E-isomer (9)	enantiomer (7)	Z-isomer (8)
1	126-132	2.7	19.1	63.8	17.0
2	132-134	2.4	19.7	64.9	15.3
3	134-138	1.6	19.9	67.1	13.0
4	138-190	1.0	20.3	70.6	9.1

Table 3.4 Yields and isomer ratios of fractions obtained from distillation of crude 6

Attempts to effect purification of the isomers by crystallisation of the neat product at -20°C were unsuccessful: although it was possible to partially solidify fraction 1, NMR spectra of the two phases were indistinguishable.

The lower layer that remained following the methanolic work-up of experiment 22 was evaporated and analysed by NMR (Figure 3.7). Main features were: some product **6** present (2.5% based on SiCH<sub>3</sub> integral ratios), otherwise broad bands, similar to those of polystyrene, the NMR of which was run for comparison.

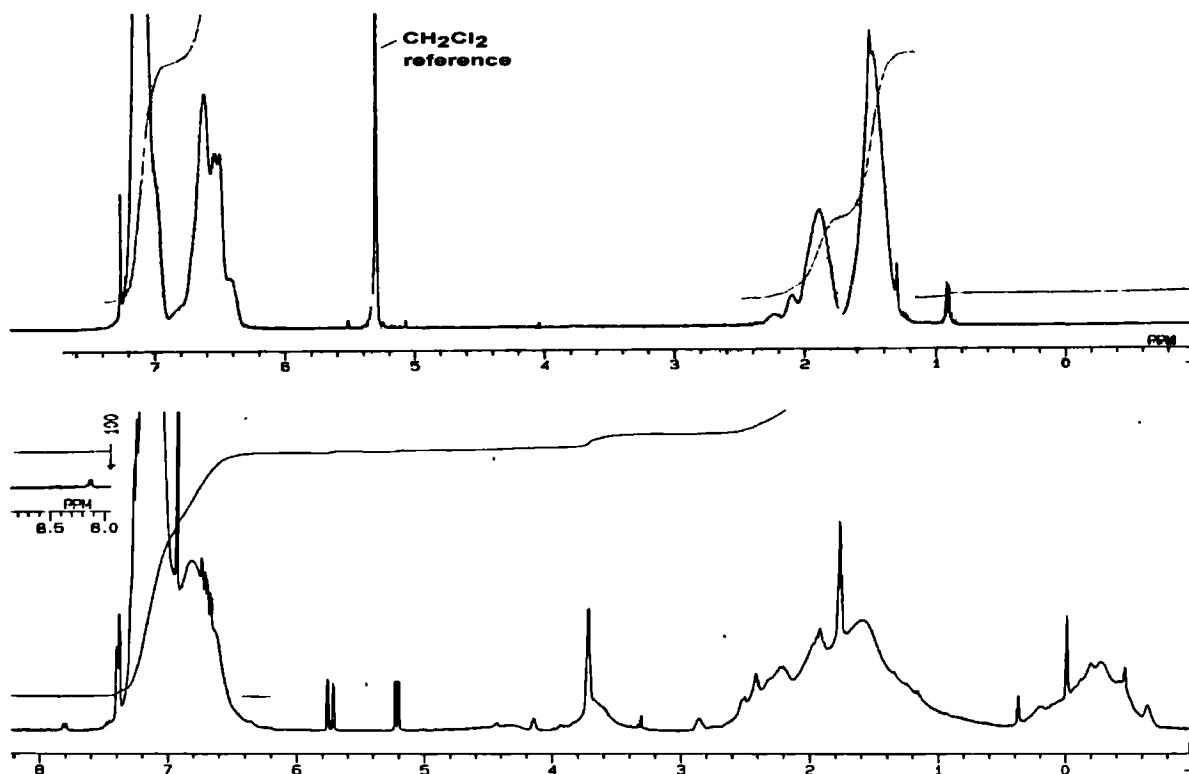


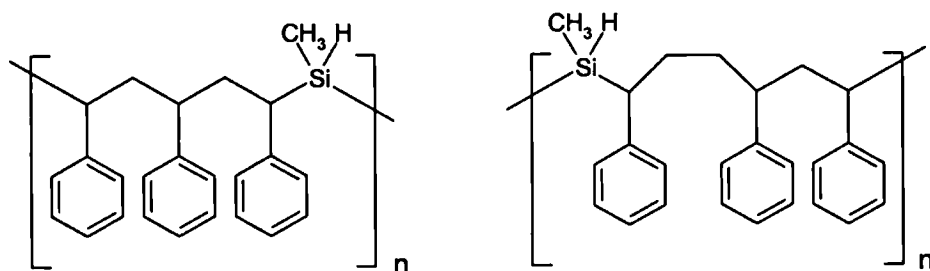
Figure 3.7 Comparison of NMR spectra of polystyrene and the precipitated residues from experiment 22

Top spectrum: polystyrene. Lower spectrum: precipitated residues (Note presence of residual styrene and THF. Also, very poor band shape – subsequent spectra recorded for diluted solution clearly showed familiar doublets for SiCH<sub>3</sub> signals of product **6**).

The broad bands of the precipitated residues spectrum were consistent with the material being polymeric, containing both the styrene and methylsilane moieties. The broad SiCH<sub>3</sub> band was centred at -0.3ppm and was correlated in the <sup>1</sup>H-<sup>13</sup>C COSY spectrum with a broad <sup>13</sup>C band (*ca.* 1ppm bandwidth) at  $\delta_C = -9$ ppm, suggesting that the methyl group

adjacent to the silicon atom was subject to shielding by adjacent phenyl groups. Whenever broad bands were present in the NMR, these always occurred in the aromatic, alkyl and SiCH<sub>3</sub> regions, implying that the polymeric material was a copolymer of these species, rather than a mixture of two polymers.

The proton integral ratio for SiCH<sub>3</sub> : CH + CH<sub>2</sub> : Ph was 3.0 : 8.5 : 14.6, which corresponded to three styrene residues per silicon methyl group. The actual polymer formed may have been a combination of the two possibilities shown in Scheme 3.14.



Scheme 3.14 Possible structures for the polymeric major product from the reaction to produce compound 6.

In all of these experiments, the NMR showed that the SiCH<sub>3</sub> signals not due to unreacted reagent appeared either as isomers of 6 (compounds 7-9, Scheme 3.1) or as broad bands due to their polymeric environment. There was never any evidence for significant amounts of the 3,4-diphenyl- analogue of 6 (Scheme 3.12), which would have given rise to discrete SiCH<sub>3</sub> signals.

### 3.1.5 Preparation of 1,1-dimethyl-2,5-diphenylsilacyclopentane (12)

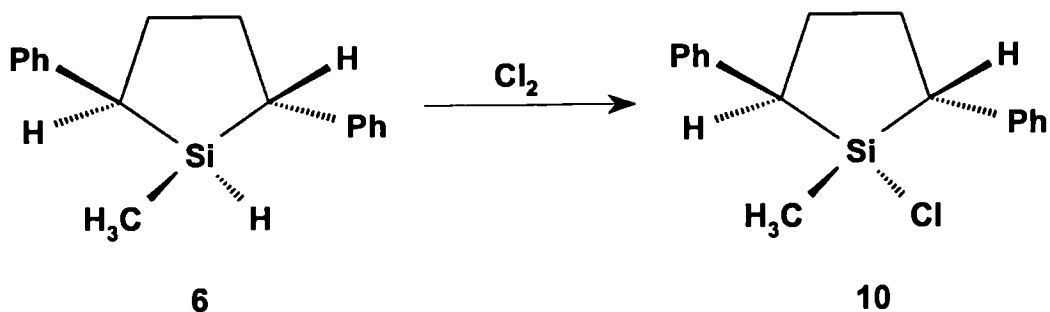
So that literature data can be compared to the yields from the reaction procedure used in this study, an analogous reaction to that discussed in Section 3.1.1 was carried out under identical conditions to prepare 1,1-dimethyl-2,5-diphenylsilacyclopentane (12). The NMR of the crude reaction product showed a smaller broad background signal in the region -1 to +1 ppm, *i.e.* a far lower concentration of SiCH<sub>3</sub> in a polymeric environment. As expected,

two isomers were formed, with the phenyl groups *E*- or *Z*- to each other (in the ratio 0.9 : 1). NMR and GC/MS showed that the ratio of *Z*- to *E*- isomers varied little between fractions and that flash chromatography would be of no use to resolve the diastereoisomers. As in the preparation of **6**, some 1,4-diphenylbutane was also formed (17% by GC peak area).

The EIMS was similar to that reported by Maruca,<sup>167</sup> (the six most abundant ions were the same in both cases). However, there was some difference between the relative abundances of the ions. Maruca reported the molecular ion having a relative intensity of 89% (base peak at *m/z* 117), compared with my results where the base peak was the molecular ion (*m/z* 117, 66% RA). Many GC/MS analyses were run on various samples of reaction mixture and product fractions, and the molecular ion was invariably the base peak. The differences may be associated with the type of mass spectrometer used. In this work, an ion trap system was employed.

After flash chromatographic purification to remove excess styrene and polymeric material, a 33% yield was obtained. This preparation was not repeated to improve the yield, which compared adequately with yields reported in the literature by Gilman and Atwell (45%),<sup>173</sup> Weyenberg *et al* (71%)<sup>155</sup> and Maruca (65%).<sup>176</sup> It seems likely that further optimisation of conditions may improve the yield. Nevertheless, although the yield now reported was lower than these literature values, it was similar enough to suggest that the poor yield obtained for the preparation of **6** was not the result of some significant deviation from the experimental conditions used by these authors. It suggests that the yield was inherently lower when the dichloromethylsilane was used as reagent rather than the dichlorodimethylsilane. The NMR clearly showed that there was far less polymeric by-product associated with the *dimethyl* preparation.

### 3.2 PREPARATION OF 1-CHLORO-1-METHYL-2,5-DIPHENYLSILACYCLOPENTANE (10)



Scheme 3.15 Preparation of racemic 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10)

Small scale reactions were conveniently carried out in an NMR tube. In a fume cupboard, chlorine was slowly bubbled through a chilled solution of the mixed isomers of **6** and the progress of the reaction was monitored at intervals by  $^1\text{H}$  NMR. The  $\text{SiCH}_3$  doublet of the major component (**7**) at 0.1 ppm was replaced by a singlet at 0.3 ppm, showing that the reaction was complete after 2h. Although the yield of this reaction was high (104% crude) initially only *ca.* 23% was obtained after vacuum distillation. The higher boiling residue was not analysed. This may have been due to hydrolysis during handling. Further preparations were carried out in a distillation apparatus, set up with a Teflon sampling / purging line to facilitate frequent monitoring by NMR with minimum exposure to the atmosphere). After the chlorination was complete, dissolved  $\text{Cl}_2$  and  $\text{HCl}$  were removed by purging the solution with  $\text{N}_2$  prior to applying the vacuum and distillation. Reasonable yields (typically 86%) of high purity products were obtained in this way. Monitoring the reaction by NMR showed an interesting difference in the rate of chlorination of the diastereoisomeric silanes and also a change in the ratio of product isomers compared with that of reactant isomers.

In analogous carbon-centred reactions, nucleophilic substitution proceeds with inversion of configuration or racemisation, depending on whether the mechanism is  $\text{S}_{\text{N}}2$  or  $\text{S}_{\text{N}}1$  respectively. In compounds having bridgehead carbon centres bearing potential leaving

groups, reactions under S<sub>N</sub>2 conditions fail to proceed, because the nucleophile cannot approach from the rear.<sup>177</sup> However, in silicon chemistry, because of the availability of the 3d orbitals, silicon can achieve a co-ordination number of 5 or 6, which allows such reactions to occur, *via* mechanisms resulting in retention of configuration at silicon.<sup>178</sup> The ability of reactions involving substitution at silicon to proceed with retention, inversion or a combination of both is well established.<sup>148</sup>

The results obtained in this work suggested that the *meso*- isomers were substituted with a combination of these mechanisms, but to different extents. Substitution in the enantiomers would be unaffected: either mechanism generates the same product.

The *Z-meso*-isomer **8** was chlorinated faster than the *E-meso*-isomer **9**, and the racemate **7** was intermediate. The reaction was carried out on a number of occasions and there was always a significant excess of the *Z-meso*- isomer product over the *E-meso*- isomer product.

In one chlorination reaction, a solution which was only partially chlorinated was left for 16 hours. The NMR was checked before the addition of chlorine, and before and after the 16 hour period, and then again after a final addition of chlorine. The data obtained are summarised in Table 3.5. During the initial chlorination, the *Z-meso*- silane isomer **8** was depleted most rapidly. After leaving the solution (saturated with chlorine) for 16 h the ratio of **7:9** reduced dramatically: from 19:8 to 2:8, indicating that the racemate **7** was chlorinated at a greater rate than the *E-meso*-isomer **9**.

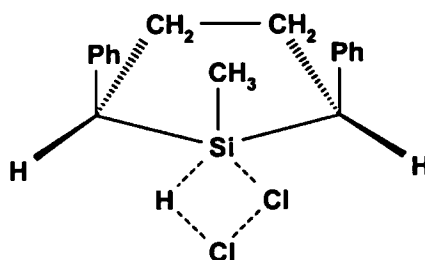
These data show that the order of ease of chlorination was *Z-meso*- > racemate > *E-meso*-. The significant increase in the *Z-meso*- : *E-meso*- isomer ratio of the product (24:8) compared with that of the reactant (15:20) suggests that the *E-meso*- silane isomer was more prone to inversion.

	silane isomers % of total			chlorosilane isomers % of total		
	<i>E</i> -meso-isomer (9)	<i>racemate</i> (7)	<i>Z</i> -meso-isomer (8)	<i>E</i> -meso-isomer	<i>racemate</i>	<i>Z</i> -meso-isomer
Before chlorination	20	66	15	0	0	0
After initial chlorination	8	19	3	10	49	11
After leaving solution 16 h.	(8) <sup>note 1</sup>	(2) <sup>note 1</sup>	nd	nd	nd	nd
After final chlorination	0	0	0	8	68	24

Table 3.5 Relative concentrations of reagent silane isomers and chlorosilane product isomers, based on <sup>1</sup>H NMR integrals.

Note 1. complete NMR data were not obtained. These values represent the ratio of the concentrations of 9 and 7. nd = not determined.

These results can be interpreted in the light of the reaction mechanisms mentioned above. Approach of chlorine from the same face as the SiH bond is clearly more facile in the less hindered isomer 8, which is why this isomer was depleted most rapidly. This is shown in Scheme 3.16.



Scheme 3.16 Possible reaction intermediate for the substitution of the less hindered silane isomer, 8, by chlorine.

This isomer was chlorinated with predominantly, if not exclusively, retention of configuration. The more hindered (with regard to same-face substitution) isomer, 9, appeared to have been chlorinated with a degree of inversion of configuration, suggesting that a mechanism similar to the carbon S<sub>N</sub>2 mechanism had occurred.



The EIMS and NMR spectrum of the crude product were consistent with the compound having the expected structure and the  $^1\text{H}$  NMR spectrum was improved only slightly by distillation. The presence of isomers complicated the spectrum, but a small sample of the chromatographically purified **7** was used to prepare a sample of **10**.

The  $^1\text{H}$  NMR spectrum of **10** was more simple than that of the precursor, having two distinct doublets of quartets, centred at 1.92 and 2.12 ppm, presumably due to two of the four  $\text{CH}_2$  protons. These would be expected to be two protons in comparable environments, *i.e.* vicinal and *E*- to each other. Because no coupling to  $\text{CH}_3$  was expected, the quartets were attributed to coupling to the three adjacent protons with similar coupling constants. One of the two  $\text{CH}(\text{Ph})$  signals was observed as a doublet of doublets at 2.86 ppm, the other was probably at 2.4 or 2.5 ppm, slightly obscured by one of the  $\text{CH}_2$  signals. The remaining two  $\text{CH}_2$  signals were more complex, between 2.4 and 2.5 ppm. The  $^1\text{H}$ - $^1\text{H}$  COSY spectrum showed the expected multiple coupling that gave rise to the complex  $^1\text{H}$  spectrum.

The  $^{13}\text{C}$  spectrum, detailed in the experimental section, fitted reasonably well with the proposed structure and was complemented by the DEPT spectrum. Two *ipso*-C atoms were present (the two phenyl groups of the expected isomer being in different environments), aromatic CH signals, and two CH bands around 39 ppm. Only one  $\text{CH}_2$  signal was apparent, at 31.3 ppm, whereas two may have been expected. However, these carbon atoms would be in very similar environments, so the coincidence of the two  $\text{CH}_2$  signals may not be so surprising.

The  $^{13}\text{C}$ - $^1\text{H}$  COSY spectrum confirmed the coupling between the carbon atoms and the protons assigned to the two CH groups. A weaker carbon signal in the same range, at 37.8 ppm, was coupled to a proton at 3.0 ppm, probably due to an impurity. The  $\text{CH}_2$  band at

31.3 ppm was coupled to the protons at 1.92, 2.12, 2.41 and 2.5 ppm in accord with the proton assignments above.

An interesting feature of the  $^1\text{H}$  NMR spectrum of this compound was the large coupling constant (13 Hz) between two of the four  $\text{CH}_2$  protons and vicinal protons. As assigned above, two of the four  $\text{CH}_2$  protons each gave rise to what looked like a doublet of quartets. This could have arisen from three couplings of approximately 13 Hz and one of 4 Hz. It would appear that a  $\text{CH}_2$  proton was coupled to two adjacent  $\text{CH}_2$  protons and to one adjacent CH proton, as well as the expected geminal coupling. This situation would give the observed multiplicity and pattern but requires an explanation for the large coupling constants. According to the modified Karplus equation for geminal couplings,<sup>174</sup> a coupling constant of about  $J_{\text{gem}} \approx 12$  to 18 Hz would be expected between the two protons of the  $\text{CH}_2$  group. However, this value is higher than might be expected from the vicinal protons. A simple model of cyclopentane gives a planar ring, so that, according to the Karplus equation, coupling to the vicinal protons would be *ca.* 8 Hz for the *Z*- protons (bond angle  $\theta \approx 0^\circ$ ), and *ca.* 4 Hz for the *E*- protons ( $\theta \approx 120^\circ$ ). Cyclopentane is normally puckered, to an extent which offers a balance between relieving bond angle strain (Baeyer strain) and Pitzer strain.<sup>179</sup> The molecule is not fixed in a rigid conformation and the pucker moves around the ring as a wave motion. In practice; observed vicinal coupling constants for cyclopentane are  $J_Z \approx 8$  Hz,  $J_E \approx 0$  Hz, corresponding to bond angles of  $\theta \approx 0^\circ$  and  $90^\circ$  respectively.<sup>174</sup> In the silacyclopentane, the increased Si-C bond length and the repulsion of adjacent groups is expected to increase the puckering of the ring. The conformational rigidity that is expected to be present, along with vicinal bond angles that are no longer at  $\approx 0^\circ$  and  $\approx 120^\circ$ , may account for an increase in one coupling constant, but this could well be at the expense of the other. The observed high coupling constants remain unexplained.

## **CHAPTER 4**

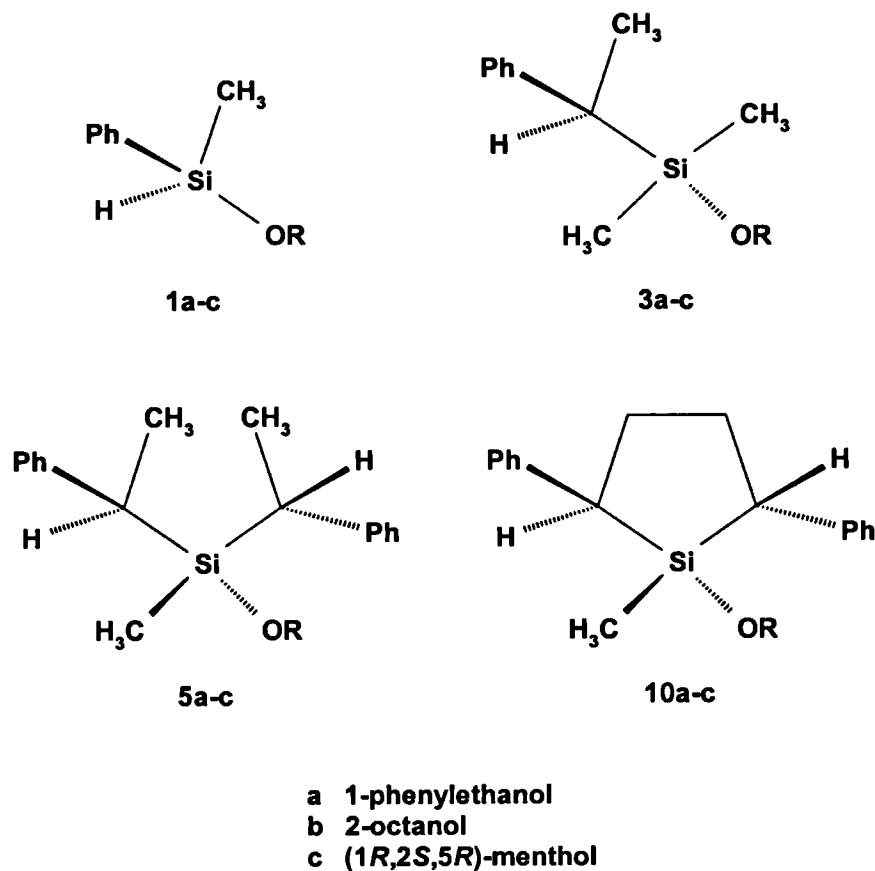
### **REACTION OF CHIRAL CHLOROSILANES WITH CHIRAL ALCOHOLS AND SEPARATION OF THE DIASTEREOISOMERIC PRODUCTS**

#### **4.1 PREPARATION, ISOLATION AND CHARACTERISATION OF DIASTEREOISOMERIC SILYL ETHERS**

Three alcohols were selected as models for the majority of this work. The reasons for their selection and their structures were given in the Introduction (1.3.4).

The chlorosilanes utilised in this work were all used in racemic form, the main objectives being to prepare diastereoisomeric derivatives, to assess their ease of formation and to evaluate chromatographic and spectroscopic means of distinguishing them. Any promising reagent would have to be produced in homochiral form, either by stereochemical synthesis or by resolution.

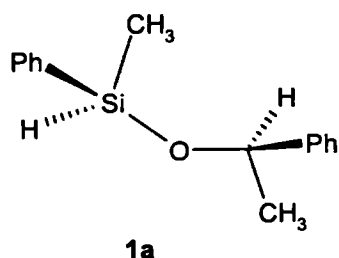
The alkoxysilanes generated were numbered on the basis of their parent chlorosilanes **1**, **3**, **5** and **10** and the alcohols, as shown in Scheme 4.1.



Scheme 4.1 Diastereoisomeric alkoxy silanes investigated in this work

In the chemical structures depicted here, one stereochemical form may be shown, but in general this should be taken to represent a mixture of all the possible stereoisomers, unless specifically noted to the contrary.

#### 4.1.1 *Methylphenylsilyl 1-phenethyl ether (1a)*

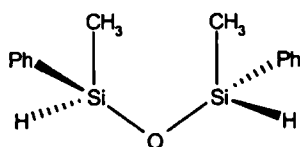


The reaction of racemic chlorosilane **1** with racemic 1-phenylethanol was very slow (no product seen by NMR after 20 min at 25°C), but proceeded rapidly (to completion in less than 5 min) on addition of pyridine. NMR showed that both diastereoisomers were produced to equal extents.

The reason for the increase in reaction rate on addition of pyridine was due to the ability of pyridine to remove the HCl formed in the reaction and/or to catalyse the reaction. The use of acid or base catalysts in similar silyl ether formation has been noted by Poole.<sup>180</sup> In

particular, when using trimethylchlorosilane as reagent, pyridine or alkylamines caused reactions to proceed much faster. In the preparation of **1a**, the distinct increase in the rate of reaction on addition of pyridine suggested that there was a strong catalytic effect.

Whereas, as is shown later, aqueous washing was an effective way of removing pyridine from the alkoxysilanes **3a-c**, **5a-c** and **10a-c**, compound **1a** was far more susceptible to hydrolysis. Three products of hydrolysis were apparent by NMR and GC/MS. GC and EIMS analysis after 24 h provided evidence that these compounds were 1-phenylethanol, methylphenylsilanol and the predominant product, 1,3-dimethyl-1,3-diphenyldisiloxane (Scheme 4.2).



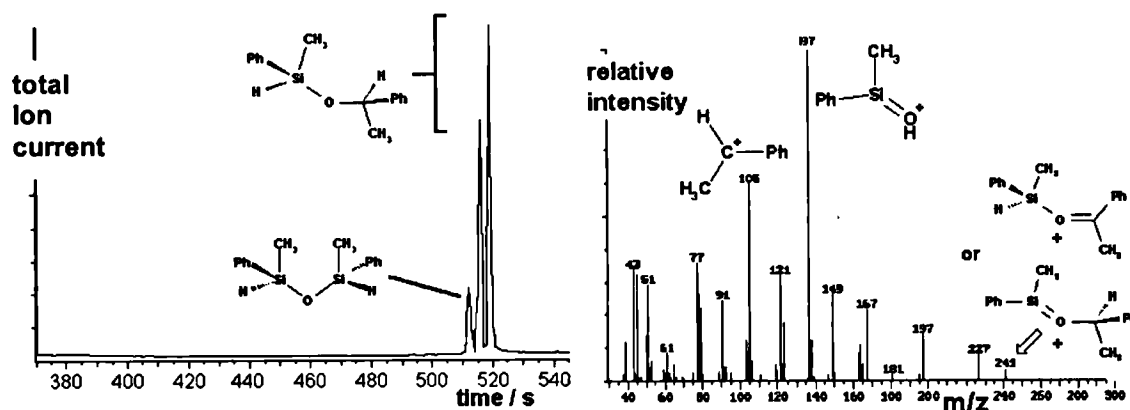
Scheme 4.2 1,3-dimethyl-1,3-diphenyldisiloxane

This disiloxane had a low RA molecular ion ( $m/z$  258), and low RA fragments  $[M-1]^+$  and  $[M-15]^+$ . Higher abundance EIMS fragments of  $m/z$  179  $[M-79]^+$  (76%) and 165  $[M-93]^+$  (100%) were probably the result of rearrangements of the two largest fragments ( $m/z$  257 (12% RA) and 243 (9% RA)) followed by loss of benzene.

It is reasonable to expect that 1,3-dimethyl-1,3-diphenyldisiloxane was formed as two diastereoisomers. The fact that only one peak was seen in the GC was probably the result of the greater difficulty in resolving diastereoisomers of this type (*i.e.* having chiral centres at the two silicon atoms). The inability of previous workers (Feibush and Spialter<sup>181</sup>) to resolve disiloxanes was discussed in the Introduction.

The preparation of **1a** was repeated and the GC/MS analysis of the reaction mixture obtained. The two diastereoisomers of **1a** were separated with separation factor,  $\alpha = 1.006$  and peak resolution,  $R_s = 1.30$ . They gave indistinguishable fragmentation patterns as would be expected from this compound. No molecular ion was apparent, but there were

$[M-1]^+$ ,  $[M-15]^+$ , and  $[M-105]^+$  fragments arising from the loss of  $H^\cdot$ ,  $CH_3^\cdot$ , and  $CHCH_3Ph^\cdot$ , the latter probably leaving  $[PhSiCH_3=OH]^+$ , the base peak. The GC and mass spectrum is shown in Figure 4.1.



1. GC of Diastereoisomer Separation  
Structure of one diastereoisomer shown

2. Electron Impact Mass Spectrum of  
either diastereoisomer

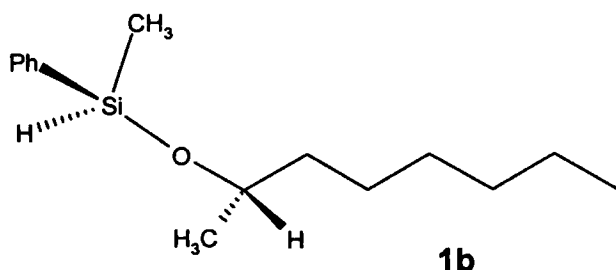
Figure 4.1 GC/MS of Methylphenylsilyl 1-phenethyl ether (1a)

Trial attempts were made to purify the products by chromatography. TLC was used (silica plate, eluted with hexane / dichloromethane 1:1 v/v), whereupon the major component eluted with the solvent front. Silica from the solvent front region was scraped from the plate, extracted with ethyl acetate, and analysed by GC/MS. A single peak resulted, corresponding to the putative disiloxane  $(PhCH_3SiH)_2O$ . To investigate if this was the result of hydrolysis on the plate, a second plate was spotted with the product mixture, but not developed. The plate was blown dry, the spotted region scraped off and extracted and analysed as before. The GC/MS clearly showed that the majority of the product had decomposed to the disiloxane and 1-phenylethanol.

A similar experiment was performed with HPLC. A column packed with silica, which had been washed with > 100 column volumes of dry solvent, was used to chromatograph the product mixture. A single peak was produced, at  $t_R$  9.6 min. This fraction was collected, and analysed by GC/MS. Again, a single peak resulted, corresponding to the disiloxane  $(PhCH_3SiH)_2O$ .

In conclusion, the silyl ether **1a** was readily formed, provided that a base was present. The two diastereoisomers were baseline resolved by GC and gave EIMS and NMR data that were consistent with the structure for the product. Any further manipulation of this particular product was difficult, owing to its ease of hydrolysis. Presumably, hydrolysis would also occur in the ethers derived from the other alcohols, although this was not examined in these cases. Hydrolysis would be a source of problem if chloromethylphenylsilane (**1**) or similar chlorosilanes were to be used as an analytical reagent.

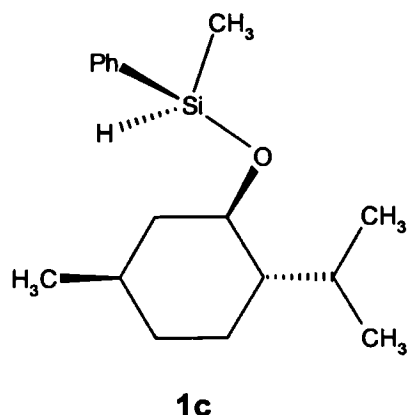
#### 4.1.2 Methylphenylsilyl 2-octyl ether (**1b**)



$^1\text{H}$  NMR of the reaction products of (*S*)-(+)-2-octanol and racemic chloromethylphenylsilane (**1**) showed that the two diastereoisomers of methylphenylsilyl 2-octyl ether (**1b**)

were formed, and were present in equal proportions. Unlike the other diastereoisomeric ethers formed from chlorosilane **1** and most of the other diastereoisomeric ethers formed from chlorosilanes **3**, **5** and **10**, the two  $\text{SiCH}_3$  groups were isochronous. However, the diastereoisomeric  $\text{C}_1$ -methyl proton signals were distinct ( $\Delta\delta_{\text{H}} = 0.04$  ppm).

The GC analysis resolved the two diastereoisomers and confirmed the diastereoisomer ratio of 1 : 1. The two diastereoisomers of **1b** were separated with separation factor,  $\alpha = 1.006$  and peak resolution,  $R_s = 1.41$ . There was also a considerable amount (15%) of a later-running component that appeared (by EIMS) to be the disiloxane,  $(\text{PhSiHCH}_3)_2\text{O}$ , as described in the discussion of **1a**. Again, although expected to be present as two diastereoisomers, only one GC peak was seen.



$^1\text{H}$  NMR of the reaction products of (1*R*, 2*S*, 5*R*)-menthol and racemic chloromethylphenylsilane (**1**) clearly showed that the two diastereoisomers of methylphenylsilyl menthyl ether (**1c**) were formed, in equal amounts.

The diastereoisomers were not resolved by GC (method B). The EIMS of **1c** was similar to that of **1a-b**, particularly with regard to the high abundance fragment,  $[\text{PhSiCH}_3=\text{OH}]^+$ . This was the base peak in **1a-b**, and 93% in **1c**. The base peak in **1c** was a fragment with  $m/z$  41, presumably being  $[\text{C}_3\text{H}_5]^+$  from the isopropyl group of menthol. Another difference in **1c** was the ion with  $m/z$  198, perhaps due to loss of benzene from the molecular ion.

A prominent ion with  $m/z$  121 (38 to 72%) was present in the EIMS of methylphenylsilyl ethers **1a-c**. This was believed to be  $[\text{PhSiHCH}_3]^+$ . This was also the proposed structure for fragments observed in the EIMS of silanes **2**, **4** (base peak) and **6**, which were formed after rearrangement (Section 2.2).

In conclusion, the silyl ethers **1a-c** were all readily formed, provided that a base was present. NMR and EIMS data for products **1a-c** was satisfactory.  $^1\text{H}$  NMR of the reaction mixtures of products **1a-c** clearly showed that the two diastereoisomers of each product were formed to equal extents. In the EIMS,  $[\text{PhSiCH}_3=\text{OH}]^+$  was the base peak or a major ion in all compounds **1a-c**.



**1a** was easily hydrolysed, and **1b-c** were expected to behave similarly. Whereas the related diastereoisomeric ethers **1a-b** were resolved by GC (method B), those of **1c** were not. These data are summarised in Table 4.1.

	retention time, $t_R$ /s	separation factor, $\alpha$	peak resolution, $R_s$
<b>1a</b>	516, 519	1.006	1.30
<b>1b</b>	499, 502	1.006	1.41
<b>1c</b>	534	not separated	-

Table 4.1 Summary of gas chromatographic data for compounds **1a-c**

As discussed in the Introduction, kinetic resolution (where one enantiomer of the reagent reacts preferentially with one enantiomer of the substrate) leads to erroneous results when a homochiral reagent is used to determine the enantiomeric purity of a substrate analyte. Only in the absence of kinetic resolution does the diastereoisomer ratio represent the enantiomeric purity of the analyte.

An added complication in the case of reagent **1** was discussed earlier; the mechanism of substitution at silicon may involve retention of configuration, inversion or a combination of the two mechanisms. These two effects will manifest themselves in different ways, depending on whether the reagents and substrates were racemic or homochiral. Table 4.2 summarises the possibilities that will arise in the most likely situations.

	rac X	rac Y	prod	rac X	hom Y	prod	hom X	hom Y	prod
1. Only one mechanism of substitution at Silicon, <i>e.g.</i> retention									
a) No kinetic resolution	R	R	RR	R	R	RR	R	R	RR
	R	S	RS						
	S	R	SR	S	R	SR			
	S	S	SS						
b) Kinetic resolution, <i>e.g.</i> higher rate of reaction when reagent and substrate have same absolute configuration	R	R	RR	R	R	RR	R	R	RR
	R	S	(RS)	see	notes	1 and 2			
	S	R	(SR)	S	R	(SR)			
	S	S	SS						
2. Reaction proceeds by two mechanisms, <i>e.g.</i> retention, with some inversion, but no kinetic resolution	R	R	RR	R	R	RR	R	R	RR
	R	R	(SR)	R	R	(SR)	R	R	(SR)
	R	S	RS						
	R	S	(SS)						
	S	R	SR	S	R	SR			
	S	R	(RR)	S	R	(RR)			
	S	S	SS						
	S	S	(RS)						

Notes: 1. (RS) denotes that the RS product is formed to a lesser extent than the stereoisomeric alternatives  
2. The effect of kinetic resolution will only be apparent if there is a deficiency of the homochiral component

Table 4.2 Summary of stereochemical outcomes of reactions of chiral reagent (X) and chiral substrate (Y) under conditions involving kinetic resolution or different mechanisms of substitution at silicon.

Although racemic reagents were used in this study, the effect of kinetic resolution and of the different possible mechanisms of substitution at silicon were of importance for potential homochiral reagents. The table gives a simplified view of the stereochemical possibilities. If the reaction were to proceed with a combination of kinetic resolution *and* with a mixture of substitution mechanisms, the situation would become more complicated. The system could even be complicated in the absence of kinetic resolution, because it is possible for there to be a stereochemical influence on the balance of the substitution mechanisms, *e.g.* if reaction of the reagent and substrate having the same absolute configuration proceeds with a greater degree of retention of configuration than those having opposite sign.

In the examples given in Table 4.2, the two main potential problems are apparent:

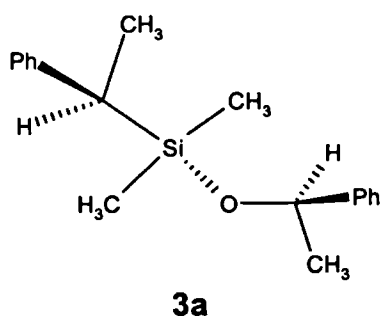
1. When there is only one mechanism of substitution operating at silicon, *e.g.* retention, but there is some degree of kinetic resolution (situation 1b), the diastereoisomeric product ratio will not reflect the original enantiomer ratio (unless both reagent and substrate are homochiral).
2. When there is no kinetic resolution, but the reaction proceeds with a mixture of retention and inversion at silicon (situation 2), the diastereoisomeric product ratio does reflect the original enantiomer ratio if either the reagent or the substrate are racemic. However, if both the reagent and substrate are homochiral, the diastereoisomeric product ratio will not reflect the original enantiomer ratio.

If either of these two situations arises, the reagent will prove unsatisfactory for routine chiral analysis, because substrates for analysis will typically have enantiomeric purity somewhere between 50% and 100%.

The experiments described above to produce compounds **1a-c**, all performed with the racemic chlorosilane, all resulted in equal amounts of each diastereoisomer. This means that there was no apparent kinetic resolution in the preparation of compound **1a-c**. Because the chlorosilane reagent was used in slight excess, the effect of kinetic resolution would have been minimal in the cases where homochiral alcohols were used (**1b-c**). Nevertheless, within the time-scale of the reaction, no kinetic resolution was apparent. The question as to whether substitution at silicon proceeds with a combination of retention and inversion cannot be answered from this work, because one component of the reaction was always racemic.

Overall, racemic chloromethylphenylsilane (**1**) reacted rapidly with alcohols in the presence of base to produce diastereoisomeric silyl ethers **1a-c** with no apparent kinetic resolution. Diastereoisomers **1a-c** were readily distinguished by NMR, **1a-b** were well resolved by GC. From the studies here, it is not possible to decide if this chlorosilane has any potential as a chiral reagent. To reiterate the potential problems: it may well be impossible to produce the reagent in homochiral form; the reagent may not have adequate stability with regard to inversion; the product diastereoisomers will not reflect the analyte enantiomer ratio if substitution at silicon proceeds with a combination of mechanisms; the products are not particularly stable to hydrolysis.

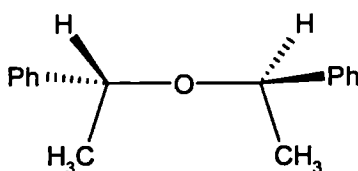
Nevertheless, **1** could be of use to confirm the homochirality of an alcohol. The convenience of the reaction and the ease of analysis are distinct advantages. A diastereoisomer ratio of 50% would result from a homochiral analyte. It may not be possible to analyse compounds with lower enantiomeric purity.



## a) attempted reaction in absence of base

The reaction of **3** with (±)-1-phenylethanol was first attempted in the absence of base. After 16 hours at 25°C, it was evident from both the NMR and GC/MS that little reaction had occurred. After 6 days, NMR showed that the reagents were still present at about 50% of their initial concentration. The GC/MS provided valuable information on the compounds produced. A small amount of the expected product was apparent (8% total peak area), with a GC retention time (559 s) and EIMS similar to that of the other two silyl ethers of this chlorosilane (**3b-c**), having significant ions at  $m/z$  75 ( $[(CH_3)_2SiOH]^+$ , 100% RA), and 179 ( $[PhCHCH_3OSi(CH_3)_2]^+$ , *i.e.*  $[M-105]^+$ ).

Some interesting by-products of the reaction included two compounds that eluted at 504 and 508 s which gave near-identical EIMS data and were probably due to the diastereoisomeric dialkyl ether, di-(1-phenylethyl)ether shown in Scheme 4.3.

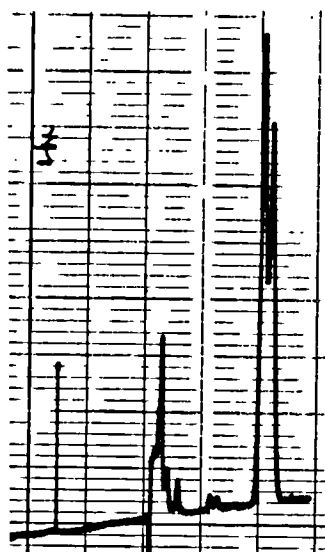


Scheme 4.3 Di-(1-phenylethyl)ether formed as a by-product in the preparation of **3a**

Another compound which was produced was apparently the disiloxane dimer,  $(PhCHCH_3Si(CH_3)_2)_2O$ , which eluted as one band at 625 s. The structure was proposed from the EIMS data, particularly from the  $[M-15]^+$  and  $[M-105]$  (100% RA) fragments. This by-product was presumably formed as two diastereoisomers, but, as in the case of the disiloxane dimers formed from chlorosilane **1** (*i.e.*  $(PhSiHCH_3)_2O$ ) these were not resolved by GC (method B).

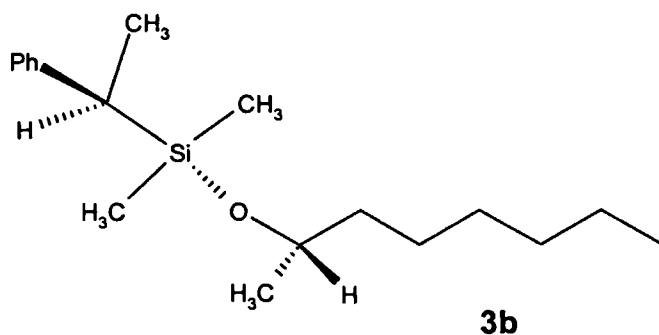
*b) reaction in presence of pyridine*

As found for other reactions, the silylether was readily formed, provided that a base was present. The diastereoisomers were not resolved by GC (method B) and gave EIMS and NMR data that were consistent with the structure of the product. GC/MS (relative peak areas, uncorrected for response factor) underestimated the concentration of the residual 1-phenylethanol starting material. In this case GC/MS analysis gave a relative peak area of 12% of 1-phenylethanol in the mixture, whereas NMR provided the more accurate value of 33%.



The two diastereoisomers of **3a** were not resolved by GC (method B) but were partially separated by HPLC (5% DCM / hexane on silica, Figure 4.2). The HPLC separation factor was  $\alpha = 1.08$  and peak resolution,  $R_s \approx 0.7$ . Fractions collected from the HPLC were re-analysed by GC and found to run concomitantly, confirming the inability of GC to resolve these diastereoisomers under the conditions described.

Figure 4.2 HPLC Partial separation of diastereoisomers of **3a**.

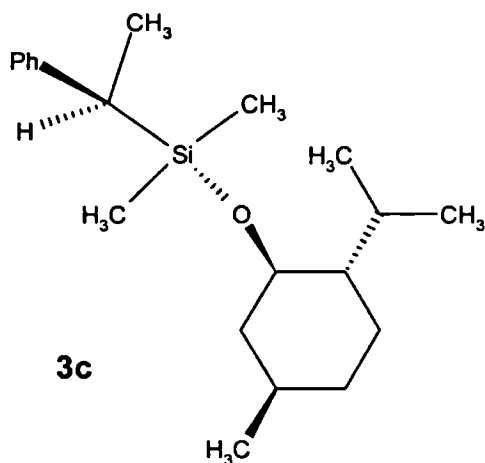


In the reaction of **3** and (*S*)-(+)-2-octanol in the presence of base, the NMR spectrum gave good evidence that the expected diastereoisomeric silyl ethers were formed, in equal proportions, in much the same way

as the 1-phenylethanol derivatives (**3a**). Again, the two NMR signals from the diastereotopic SiCH<sub>3</sub> groups of the chlorosilane became four equal-integral singlets in the ether.

The EIMS corresponded well with the expected product, and was quite similar to that obtained from the 1-phenylethanol derivative, particularly the presence of fragments with  $m/z$  [M-105]<sup>+</sup>, and 75.

The diastereoisomers were not resolved by GC (method B) but were partially separated by HPLC (5% DCM / hexane on silica, separation factor,  $\alpha = 1.05$ , but peak resolution,  $R_s$  not quantifiable). Fractions collected from the HPLC were re-analysed by GC and found to run concomitantly, confirming the inability of GC to resolve these diastereoisomers under the conditions described.



The NMR spectrum, although complicated in the aliphatic region, provided good evidence that the expected diastereoisomeric silyl ethers were formed, and in equal proportions. In particular, the two signals from the diastereotopic  $\text{SiCH}_3$  groups of the chlorosilane, gave four equal-integral singlets in the ether.

In the GC/MS no molecular ion was apparent, but a low-abundance  $[\text{M}-15]^+$  ion, characteristic of the loss of a methyl radical from the initial molecular ion, was present. Loss of  $[\text{PhCHCH}_3]^+$  to give an ion of  $m/z$  213 (27% RA) was probably followed by the loss of a neutral elimination product of menthol to result in the base peak at  $m/z$  75. These two fragments were also major features of the 1-phenylethanol and 2-octanol derivatives (**3a-b**). There were two fragments which were more difficult to assign, having  $m/z$  137 (20%) and 81 (29%). These were not seen to any significant extent in the related ethers, (**3a-b**). In the EIMS of the methylphenylsilyl ethers (**1a-c**), the base peak was normally at  $m/z$  137, and was attributed to  $[\text{PhCH}_3\text{SiOH}]^+$ . This was a likely structure for the  $m/z$  137 peak found here, which would require some rearrangement. The formation of the fragment at  $m/z$  81 remained unexplained.

The diastereoisomers were not resolved by GC (method B) or by HPLC (5% DCM / hexane on silica).

## 4.1.8

*Summary of discussion of compounds 3a-c.*

In conclusion, the silyl ethers **3a-c** were all readily formed, provided that a base was present. NMR and EIMS data for products **3a-c** was satisfactory.  $[(\text{CH}_3)_2\text{SiOH}]^+$  was the



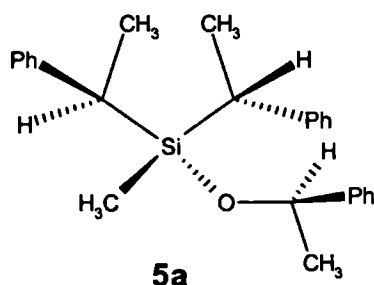
base peak and  $[M-105]^+$  was a major fragment in all compounds **3a-c**. The NMR spectrum distinguished the two diastereoisomers of **3a-c** and showed that they were formed to equal extents.

None of the diastereoisomeric ethers formed from chlorosilane **3**, *i.e.* **3a-c** were resolved by GC (method B). The diastereoisomeric ethers **3a-b**, but not **3c**, were partially separated by HPLC (5% DCM / hexane on silica). Fractions from the HPLC were re-analysed by GC and found to run concomitantly, confirming that they were the diastereoisomers, and that GC failed to resolve them. The HPLC data are summarised in Table 4.3. The retention time of **3c** was rather low compared with that of **3a** and **3b**. This may have indicated that the silylether oxygen atom played a significant part in the chromatographic retention mechanism, with the menthyl group hindering access to the oxygen atom to a greater extent than the phenethyl or octyl groups of **3a** and **3b**.

	retention time, $t_R$ /min	separation factor, $\alpha$	peak resolution, $R_s$
<b>3a</b>	17.9, 18.7	1.08	$\approx 0.7$
<b>3b</b>	17.0, 17.5	1.06	not quantifiable
<b>3c</b>	12.6	not separated	-

Table 4.3      Summary of HPLC data for compounds **3a-c**

The inability to separate any of the diastereoisomeric pairs by GC was compared with the partial resolutions obtained for compounds **1a** and **1b** (Table 4.1). It seems likely that the reduced differentiation of **3a** and **3b** is a result of the increased chain length between the two chiral centres, as discussed in the introduction.



Following the reaction of **5** with ( $\pm$ )-1-phenylethanol, GC resolved three peaks that had EIMS corresponding to **5a** product isomers. Interpretation of the NMR of the product mixture was complicated by the silyl ethers resulting from isomeric impurities of **5** and the presence of diastereotopic protons in the product.

As discussed in Section 2.2, chlorosilane **5** was formed as a mixture of four stereoisomers. The structures, shown in Scheme 2.3, were the two symmetric *meso*-forms (4i and 4ii) and two enantiomeric forms (4iii and 4iv). In the absence of kinetic resolution, the (1*R*, 2*R*, 5*R*)-enantiomer of **5** would react with racemic alcohol to yield two products trivially described as (1*R*, 2*R*, 5*R*)-(*R*) and (1*R*, 2*R*, 5*R*)-(*S*). Similarly, the (1*S*, 2*S*, 5*S*)-enantiomer of **5** would yield (1*S*, 2*S*, 5*S*)-(*R*) and (1*S*, 2*S*, 5*S*)-(*S*). These four diastereoisomeric products are two racemates. A similar situation exists for the two *meso*-isomers of **5**, which also yields two diastereoisomers. Accordingly, in the absence of kinetic resolution, four diastereoisomeric products, in equal proportions, were expected from the reaction of **5** with racemic alcohols.

GC of the product mixture resolved three peaks, which had EIMS corresponding to product isomers. The three peaks were well separated by GC, having  $\alpha_{1,2} = 1.019$   $R_{s(1,2)} = 2.18$  and  $\alpha_{2,3} = 1.020$ ,  $R_{s(2,3)} = 2.30$ , better than any of the diastereoisomers formed from other *chiral* chlorosilanes described above. For this reason, the three were suspected not to include the resolved diastereoisomers arising from the *chiral* chlorosilane, but to be the products of the two *meso*-chlorosilanes and the unresolved products of the (racemic) *chiral* chlorosilane.

Preparative HPLC was used to separate some of the isomeric impurities which simplified the analysis. The three fractions separated by HPLC were analysed by GC/MS and shown to correspond to the three GC peaks produced from the reaction mixture. Table 4.4 summarises the GC analysis of the product mixture, the HPLC purification of diastereoisomers, and the analysis of those HPLC fractions by GC, NMR and circular dichroism spectroscopy. Partial NMR spectra of the three HPLC fractions are compared in Figure 4.3. Selected NMR data are summarised in Table 4.5.

GC analysis of product mixture		Small-scale preparative HPLC		Analysis of fractions from small-scale preparative HPLC			
$t_R/s$	isomer %	$t_R/min$	amount.	GC		NMR	CD
				$t_R/s$	purity/%		$\Delta\epsilon/\epsilon$
902	33	13.8	med.	902	100	isomer #1	0
919	56	15.4	large	917	100	#2 and small #3	0
937	11	16.4	small	936	87	isomer #4	nd

Table 4.4 Summary of analytical data from the **5a** product mixture and from the fractions purified by HPLC.

HPLC fraction	$\delta_H/$ ppm				
	SiCH <sub>3</sub> (s)	CH <sub>3</sub> CO (d)	CH <sub>3</sub> CSi (2d)	CHSi (2q)	CHO (q)
fraction 1	-0.01	1.14	1.20, 1.30	2.13, 2.23	4.35
fraction 2	-0.14	1.20	1.23, 1.45	2.26, 2.28	4.46
+ impurity	-0.16	1.11	1.30, 1.31	2.22, 2.35	4.41
fraction 3	-0.18	1.36	1.24, 1.42	2.17, 2.24	4.70

Table 4.5 Chemical shifts of aliphatic protons in resolved diastereoisomers of **5a**

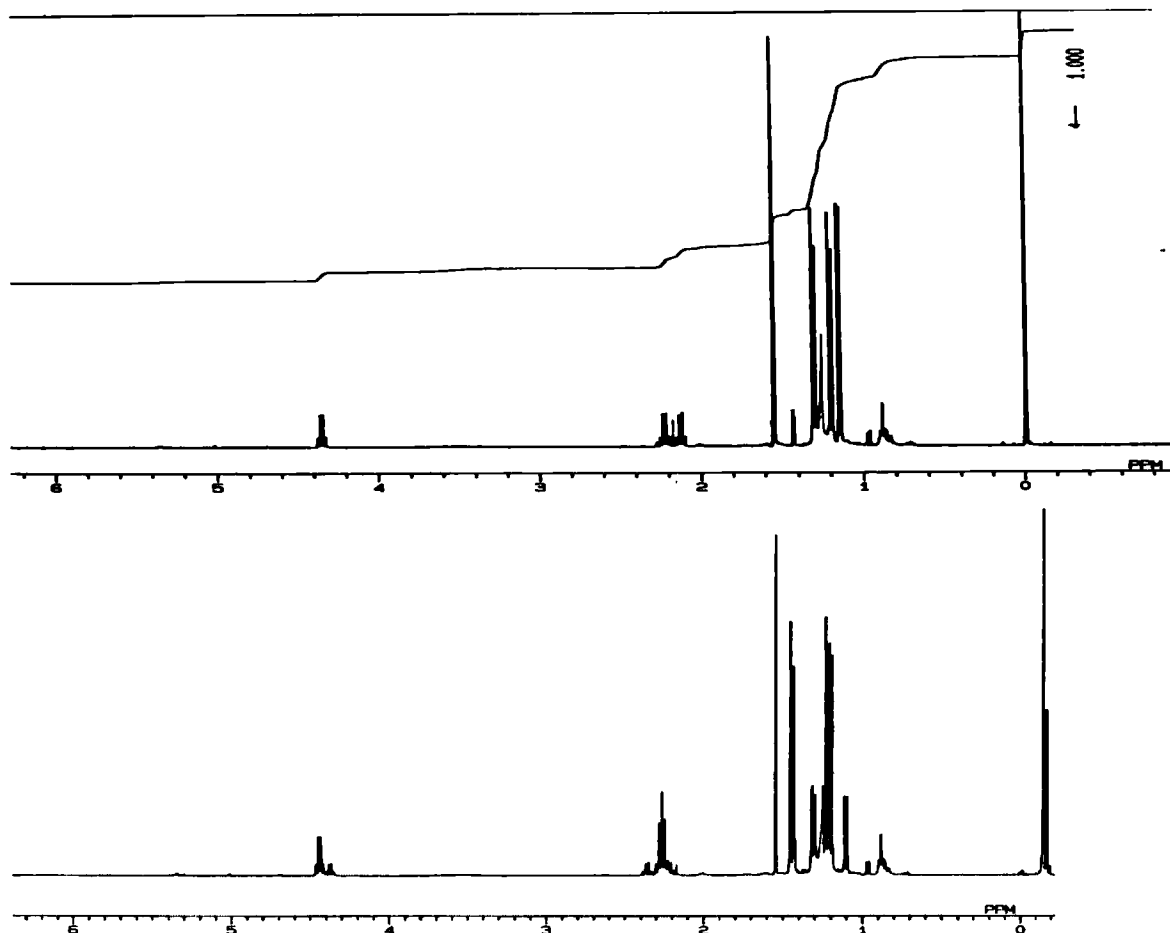


Figure 4.3  $^1\text{H}$  NMR comparison of the resolved diastereoisomers of **5a**.

Note: signal at *ca.* 1.6 ppm =  $\text{H}_2\text{O}$  in  $\text{CDCl}_3$ .

The NMR spectra of the three HPLC fractions showed the presence of the expected four diastereoisomers, there being a small isomeric impurity in the second fraction. This isomer was present at a considerably lower concentration than the major component of that fraction. The fact that one of the parent *meso*-chlorosilane isomers was a minor component suggested that the small isomeric impurity in the second fraction might be the product of one of the *meso*-chlorosilane diastereoisomers (unless there had been considerable kinetic resolution in the reaction).

However, in the chromatographic purification, reduction of the concentration of one diastereoisomer was quite possible because the process was optimised for purity of the observed resolved components. Thus significant amounts of a particular diastereoisomer

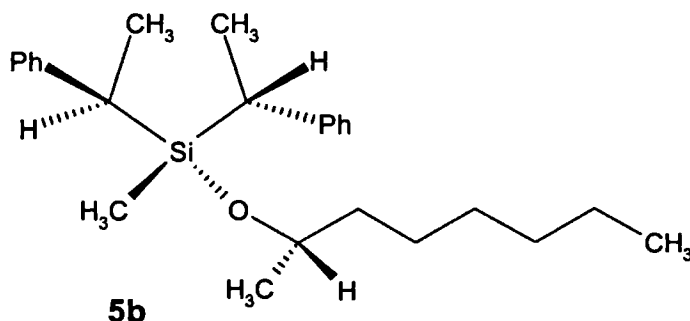
may not have been recovered, particularly if it was a minor component eluted under the leading edge or tail of a major component. The diastereoisomeric impurity coeluted with the same other major isomer in both the GC and the HPLC. The implication is that the two products derived from the (racemic) chiral chlorosilane may have been well resolved by HPLC ( $t_R = 13.8$  and  $15.4$  min). From the GC analysis of these HPLC fractions, it followed that this pair of diastereoisomers were also resolved by GC. These two diastereoisomers had  $\text{SiCH}_3$  signals at  $-0.01$  and  $-0.14$ , and the two other diastereoisomers had  $\text{SiCH}_3$  signals at  $-0.16$  and  $-0.18$ .

Alternatively, the  $\text{SiCH}_3$  shift could be used to distinguish the product diastereoisomers which originated from the *meso*-isomers of the chlorosilane, in the same way as for the parent silane, because the *meso*-isomers had extremes of chemical shift. In this case, the conclusion would be contradictory, *i.e.* the *meso*-isomers were eluted in the first and third fractions, and that the *E*-isomers coeluted in the second fraction. In this set of compounds, the NMR interpretation is complicated by the effect of the third phenyl ring introduced by the alcohol and thus the assignment of signals to particular diastereoisomers is open to question. Added to this, the  $\text{SiCH}_3$  shifts of the three diastereoisomers are all quite close.

Circular dichroism spectroscopy of the three fractions showed no CD activity. This is to be expected because both reagents used to prepare **5a** were racemic, so each diastereoisomer would have been present with its unresolved enantiomer.

In summary, while it was possible that the two diastereoisomers derived from the (racemic) chiral chlorosilane were resolved by HPLC and GC, this could not be confirmed by NMR. If the experiment was repeated with the homochiral alcohol, CD spectroscopy of the resolved diastereoisomers may provide further insight. However, the CD may be difficult to interpret, especially with the extra phenyl chromophore present in this compound.

#### 4.1.10 *Bis(1-phenethyl)silyl 2-octyl ether (5b)*



Following the reaction of **5** with (*S*)-(+)-2-octanol, GC resolved three peaks, which had EIMS corresponding to product isomers. The three peaks were well separated by GC, having

$\alpha_{1,2} = 1.017$ ,  $R_{s(1,2)} = 2.47$  and  $\alpha_{2,3} = 1.015$ ,  $R_{s(2,3)} = 2.21$ . As in the case of **5a**, the three were suspected not to include the resolved diastereoisomers arising from the *chiral* chlorosilane, but to be the products of the two *meso*-chlorosilanes and the unresolved products of the (racemic) *chiral* chlorosilane. As with the other silyl ethers derived from the chlorosilane **5**, interpretation of the NMR spectra of the product mixture was complicated by the isomeric impurities from **5** and the presence of diastereotopic protons in the product.

However, preparative HPLC separated some of the isomeric impurities and simplified the analysis. The three fractions separated by HPLC were analysed by GC/MS and shown to correspond to the three GC peaks produced from the reaction mixture. Table 4.6 summarises the GC analysis of the product mixture, the HPLC purification of diastereoisomers, and the analysis of those HPLC fractions by GC, NMR and circular dichroism spectroscopy. The CD data is expressed in terms of  $\Delta\epsilon/\epsilon$  to allow comparison of all three fractions because the accurate solution concentration was not known for the minor impurity isolated by HPLC. NMR spectra of the first two of the three HPLC fractions are compared in Figure 4.4. NMR data are summarised in Table 4.7.

GC analysis of product mixture		Small-scale preparative HPLC		Analysis of fractions from small-scale preparative HPLC			
$t_R/s$	isomer %	$t_R/min$	amount.	GC		NMR	CD $\Delta\epsilon/\epsilon$
				$t_R/s$	purity/%		
835	36	10.8	medium	820	100	isomer #1	$-7.2 \times 10^{-5}$
849	53	12.7	large	832	100	isomer #2 and #3	$+3.6 \times 10^{-5}$
862	11	13.4	small	843	97	isomer #4	$+3.2 \times 10^{-5}$

Note. The GC retention times of the HPLC fractions were lower than when the product mixture was analysed because the GC column had been shortened since the original analysis.

Table 4.6 Summary of analytical data from the **5b** product mixture and from the fractions purified by HPLC.

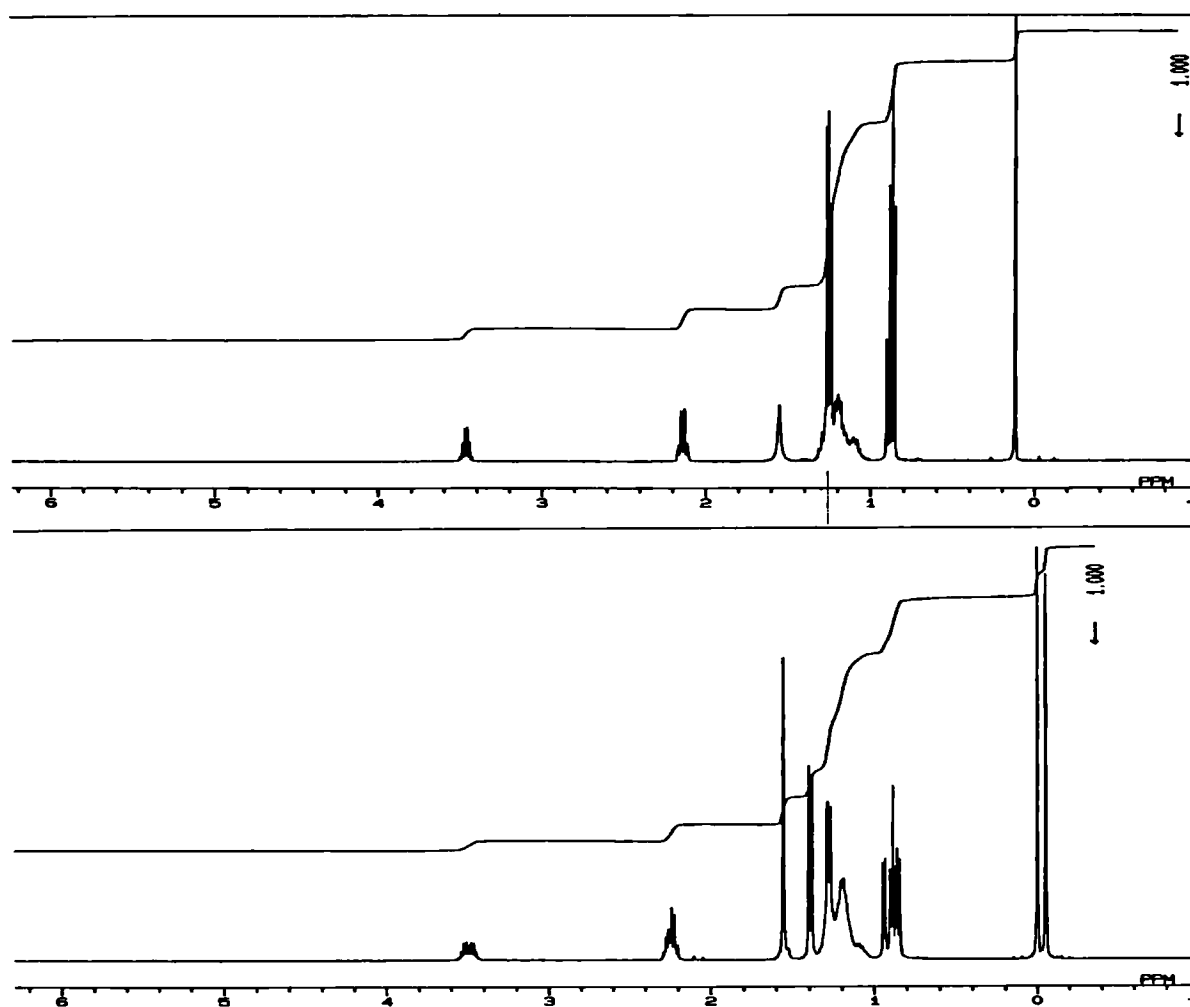


Figure 4.4  $^1\text{H}$  NMR comparison of the resolved diastereoisomers of **5b**.

HPLC fraction	$\delta_{\text{H}}$ / ppm				
	SiCH <sub>3</sub> (s)	CH <sub>3</sub> CO (d)	CH <sub>3</sub> CSi (2d)	CHSi (2q)	CHO (q)
fraction 1	0.12	0.86	1.25, 1.26	2.14, 2.14	3.46
fraction 2 (2 isomers)	-0.05, -0.05	0.85, 0.94	1.28, 1.28 1.39, 1.39	2.23, 2.23 2.25, 2.25	3.47, 3.51
fraction 3	-0.12	1.09	1.38, 1.38	2.19, 2.19	3.70

Table 4.7 Chemical shifts of aliphatic protons in the resolved diastereoisomers of **5b**

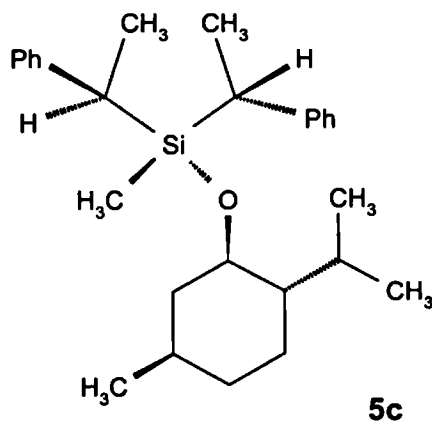
The product isomers produced three peaks in the HPLC. Three corresponding fractions were collected and found to contain the expected four diastereoisomers as evidenced by the NMR spectra (Figure 4.4). The interpretation of the NMR data from the isomers of **5b** was more simple than that for **5a**. The results from **5a** were difficult to interpret because the ratio of product isomers, which could sometimes be used to "track" which product isomer was derived from which chlorosilane isomer, was very likely biased by the selection procedure used in the chromatographic fraction collection. Also, the SiCH<sub>3</sub> shifts were quite similar for three of the four diastereoisomers, probably because of an extra shielding effect from the aromatic system of the phenethyl group. In the case of **5b**, the complication, which arose from the presence of diastereotopic protons, could be turned to advantage because the subtle differences between the spectra gave some insight into the stereochemistry of the individual diastereoisomers. Of the four stereoisomers, the first that eluted from the HPLC had the highest chemical shift for the SiCH<sub>3</sub> protons and the lowest shift for the CHO and C-1 methyl protons, while the last-eluted isomer behaved oppositely. As distinct from the situation with **5a**, these observations are self-consistent and are indicative that these isomers originated from the two *meso*-chlorosilanes **5**, the OCHCH<sub>3</sub>C<sub>6</sub>H<sub>13</sub> group being closer to the phenyl rings in the first eluted isomer, while the isomer derived from the other *meso*- chlorosilane was eluted last.



The fraction at intermediate HPLC retention time gave an NMR spectrum which would be expected for the two other diastereoisomers, *i.e.* those derived from the (racemic) chiral chlorosilane. There were two similar size sets of signals, having chemical shifts generally intermediate with respect to those of the products derived from the other *meso*-chlorosilanes. Because the two SiCH<sub>3</sub> signals were coincident in both the <sup>1</sup>H and <sup>13</sup>C spectrum, the <sup>29</sup>Si spectrum was recorded. This showed two <sup>29</sup>Si signals corresponding to the SiCH<sub>3</sub> groups of the two diastereoisomers. All other aliphatic <sup>1</sup>H signals were doubled up, with the most distinct differences between related signals from the two diastereoisomers being the C-1 methyl doublets ( $\delta\Delta=0.09$  ppm) and the CH<sub>3</sub>CHPh doublets ( $\Delta\delta=0.11$  ppm).

The CD spectra of the 3 fractions did not positively confirm the above conclusions. At *ca.* 230 nm all three fractions exhibited circular dichroism. It had been hoped that the derivatives, which originated from chlorosilanes with the *meso*-configuration would be optically inactive. This was because these diastereoisomers, although chiral, would have equal and opposite CD contributions from the key chromophores (the phenyl rings) in mirror-image environments. This may have arisen from incomplete separation of the diastereoisomers, or from the chiral group changing the conformation of the molecule, so that the two CD effects no longer compensated each other.

In summary, the NMR data suggested that the diastereoisomer mixture obtained from the HPLC originated from the racemic chiral chlorosilane, *i.e.* that derivatisation with the homochiral chlorosilane would fail to resolve racemic 2-octanol, either by GC or by HPLC under the stated conditions.



In all work on the bis(1-phenylethyl)chloromethylsilane derivatives (**5a-c**), the results were confounded by the presence of the diastereoisomeric products formed from the *meso*-chlorosilane isomers.

The complexity of the NMR spectrum made interpretation difficult, particularly as there was excess

menthol in the reaction mixture and the presence of six SiCH<sub>3</sub> singlets indicated that there was a number of related impurities. However, methyl doublets that had been shifted to higher field (0.61, 0.62) were recognisable as those of the menthyl group experiencing the diamagnetic shielding effect of the phenyl rings from the chlorosilane reagent.

Evidence from the GC/MS was more conclusive. Earlier peaks in the GC could be attributed to unreacted menthol, (PhCHCH<sub>3</sub>)<sub>2</sub> dimeric impurity from the chlorosilane reagent, and the silanol derivative of the chlorosilane. The three later-running bands in the GC had relative peak areas of 17%, 32%, and 5%, and EIMS spectra which, although not providing a molecular ion, gave a fragmentation pattern which were due to isomers of the intended product. The spectrum contained high-abundance [M-105]<sup>+</sup> fragment ions (66% RA), and the rearranged ion with m/z 137 ([PhCH<sub>3</sub>SiOH]<sup>+</sup>, 100%).

The three peaks were well separated by GC, having  $\alpha_{1,2} = 1.016$   $R_{s(1,2)} = 2.29$  and  $\alpha_{2,3} = 1.023$ ,  $R_{s(2,3)} = 3.25$ . As in the cases of **5a** and **5b**, the three were suspected not to include the resolved diastereoisomers arising from the *chiral* chlorosilane, but to be the products of the two *meso*-chlorosilanes and the unresolved products of the (racemic) *chiral* chlorosilane.

To clarify the situation regarding the nature of the diastereoisomers formed and separable by GC, the product mixture was resolved into some of its components by HPLC (summarised in Table 4.8). Two peaks predominated in the HPLC. Corresponding fractions were collected and analysed by GC/MS, which confirmed that they were the two major products seen before in the GC/MS. The minor isomer was not found in either HPLC fraction.

GC analysis of product mixture		Small-scale preparative HPLC		Analysis of fractions from small-scale preparative HPLC			
$t_R/s$	isomer %	$t_R/min$	amount.	GC		NMR	CD
				$t_R/s$	purity/%		$\Delta\epsilon/\epsilon$
975	31	12.0	medium	969	100	one isomer	$-7.5 \times 10^{-5}$
991	59	12.7	large	983	85	two isomers	$-1.0 \times 10^{-4}$
1014	9						

**Note.** The GC retention times of the HPLC fractions were lower than when the product mixture was analysed because the GC column had been shortened since the original analysis.

Table 4.8 Summary of analytical data from the **5c** product mixture and from the fractions purified by HPLC.

HPLC fraction	$\delta_H$ / ppm				
	SiCH <sub>3</sub> (s)	menthyl CH <sub>3</sub> (3d)	CH <sub>3</sub> CSi (2d)	CHSi (2q)	CHO (q)
fraction 1	0.15	0.60, 0.76, 0.81	1.23, 1.24	2.19, 2.21	3.22
fraction 2	-0.03	0.61, 0.64, 0.78	1.32, 1.32	2.25-2.23	3.28
(2 isomers) <sup>1</sup>	-0.02	0.79, 0.84, 0.87	1.40, 1.41		

Note 1. data are not separated for each diastereoisomer

Table 4.9 Chemical shifts of aliphatic protons in the resolved diastereoisomers of **5c**

The <sup>1</sup>H NMR spectra of these fractions are compared in Figure 4.5. NMR analysis of these compounds (summarised in Table 4.9) showed that the first, having a relatively low-field SiCH<sub>3</sub> signal was probably derived from the *meso*-chlorosilane isomer of **5** which had the O-menthyl group closer to the phenyl groups. The methyl groups that originated from this reagent isomer were rendered diastereotopic by reaction with menthol and produced two doublets at 1.23 and 1.24 ppm.

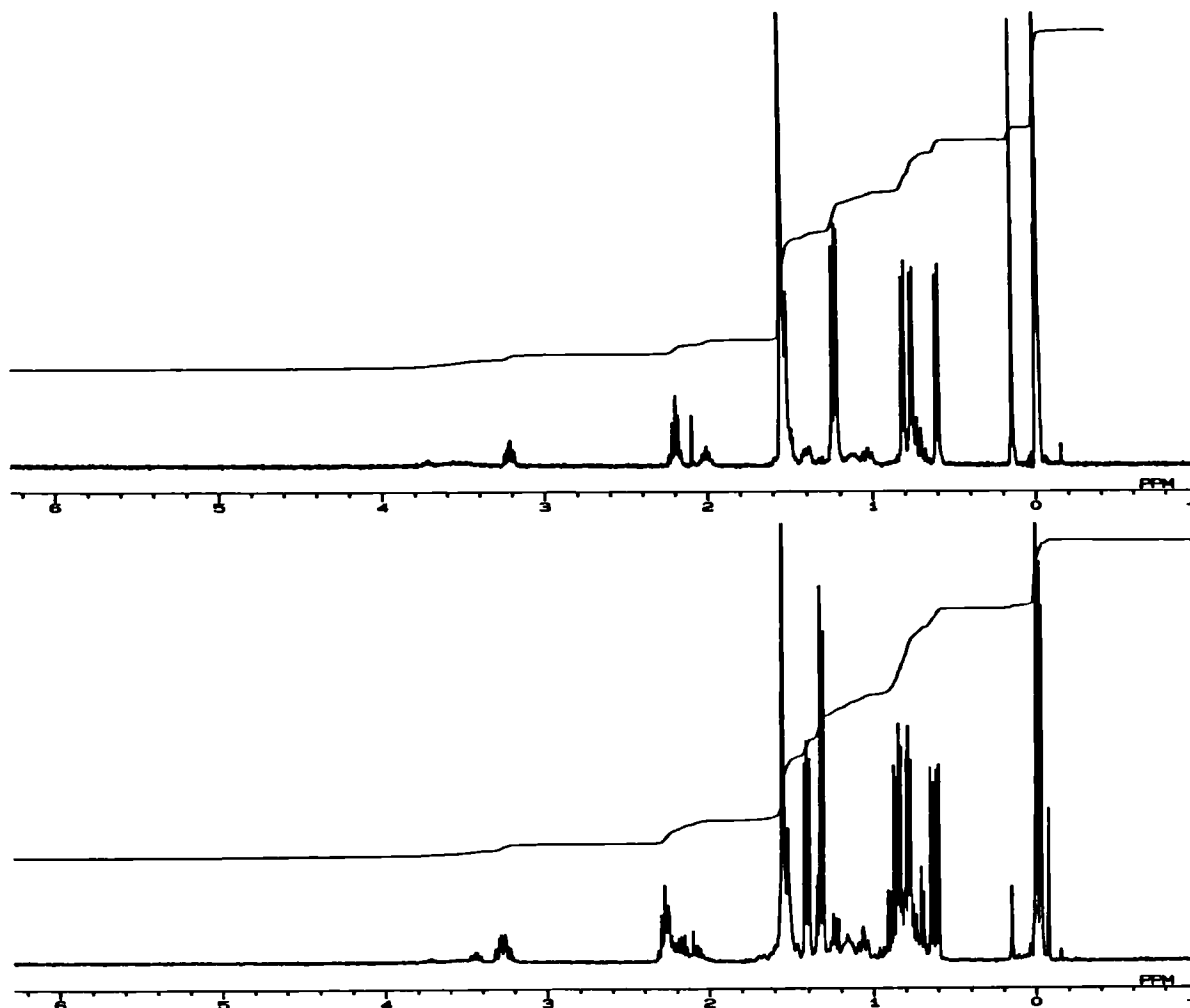


Figure 4.5  $^1\text{H}$  NMR comparison of the two HPLC fractions of **5c**.

Note: TMS present in both NMR solutions.

The second HPLC fraction provided a more complex NMR spectrum (Figure 4.5b). Two  $\text{SiCH}_3$  bands with similar height at -0.03 and -0.02 ppm indicated the presence of two isomers, their chemical shift suggesting that they were the diastereoisomeric products derived from the (racemic) chiral chlorosilane. The menthyl methyl groups appeared as six resolved doublets between 0.60 and 0.88 ppm. The methyl groups that originated from the chlorosilane reagent produced two resolved methyl doublets at 1.40 and 1.41 ppm and a doublet at 1.32 ppm. The combined integral for the pair of doublets at 1.40 and 1.41 ppm was equal to that of the doublet at 1.32 ppm, which presumably comprised two coincident methyl doublets. This was consistent with other integral ratios, and supported the conclusion that the two diastereoisomers were present in this fraction in equal amounts.

In order to obtain further evidence that this diastereoisomer mixture originated from the (racemic) chiral chlorosilane, the CD spectrum of the HPLC fractions were recorded. It was hoped that the CD of products derived from either *meso*- chlorosilane isomer would be approximately zero, on the basis that the two phenyl chromophores of any such diastereoisomer would have equal and opposite CD.

Again, the CD did not provide the expected information. Interestingly, both fractions gave a negative CD at *ca.* 230 nm. CD at this wavelength was principally due to the phenyl, not the menthyl group. Clearly, the menthyl group had a strong influence on the molecular conformation, preventing the CD data from being used in the intended way.

#### 4.1.12 *Summary of discussion of compounds 5a-c*

The silyl ethers **5a-c** were all readily formed, provided that a base was present. NMR and EIMS data for products **5a-c** was satisfactory. The rearranged ion with  $m/z$  137 ( $[\text{PhCH}_2\text{SiOH}]^+$ ) was a major fragment in all compounds **5a-c**. The NMR spectrum distinguished the two major diastereoisomers of **5a-c** and showed that they were formed to equal extents.

Preliminary evidence for the stereochemistry of the isomers resolved by GC and HPLC was based on the isomer ratio of each of the products and relating back to the isomer ratio and structures for the parent silanes assigned by NMR. The isomer ratios are compared in Table 4.10. The silane and chlorosilane isomer ratios were determined by NMR, the silyl ether isomer ratios were determined by GC and are reported in order of elution.

compound	isomer ratio
silane <b>4</b>	30 : 50 : 20
chlorosilane <b>5</b>	30 : 50 : 20
silyl ether <b>5a</b>	33 : 56 : 11
silyl ether <b>5b</b>	36 : 53 : 11
silyl ether <b>5c</b>	31 : 59 : 9

Table 4.10 Isomer ratio of silane, chlorosilane and derived silyl ethers.

The NMR spectra suggested that the diastereoisomeric products of the racemic chiral chlorosilane **5b-c** were unresolved by HPLC or by GC, even when eluted with a very slow temperature program. The CD did not provide evidence that could be used to establish which diastereoisomers had been resolved. The CD results are discussed in greater detail towards the end of this Section.

Being based on work with the racemic alcohol, the evidence for the resolution of **5a** was not conclusive. Overall, it appeared that the diastereoisomeric products of the racemic chlorosilane had probably not been resolved. If this experiment were repeated with the homochiral alcohol, rather than with the racemate, the CD may still not provide adequate evidence as to which diastereoisomers had been resolved, because of the extra phenyl chromophore.

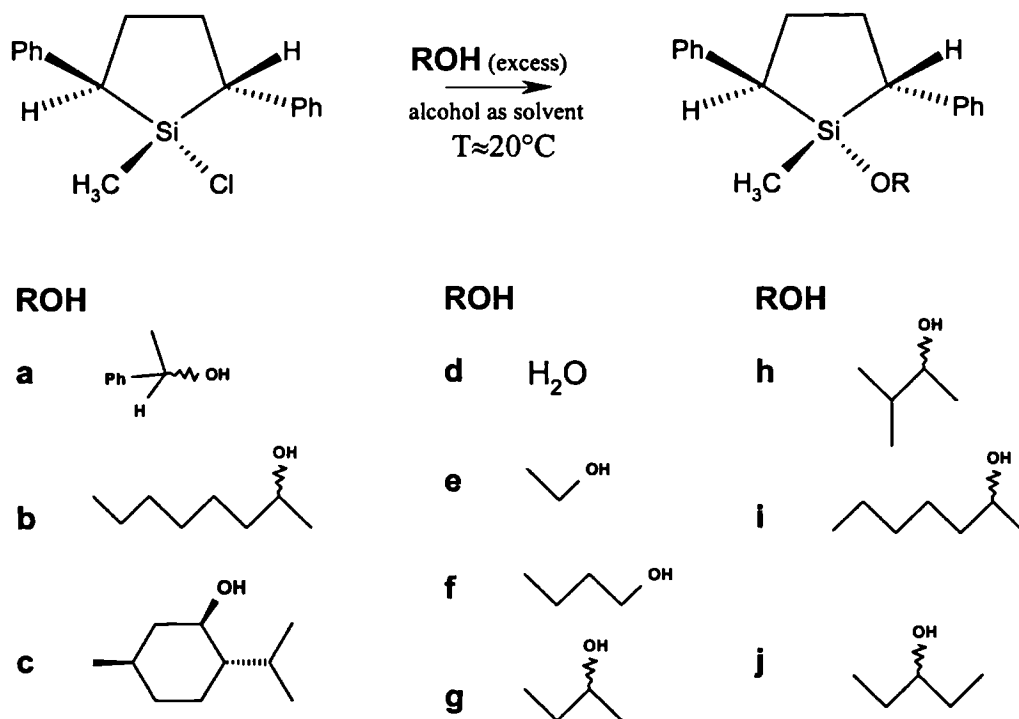
It appeared likely that the diastereoisomeric products **5a-c** which originated from the three *geometric* isomers of chlorosilane **5** were well resolved by both HPLC and GC (except in the HPLC of **5c**, where only two peaks were seen). However, the products that originated from the two enantiomers of **5** were probably unresolved by either technique under the stated conditions. The chromatographic data are summarised in Table 4.11.

	GC retention time, $t_R$ /s	HPLC retention time, $t_R$ /min
<b>5a</b>	902, 919, 937	13.8, 15.4, 16.4
<b>5b</b>	835, 849, 862,	10.8, 12.7, 13.4
<b>5c</b>	975, 991, 1014	12.0, 12.7

Table 4.11 Summary of chromatographic data for the diastereoisomeric products from chlorosilane **5**.

#### 4.1.13 Initial experiments using 1-chloro-1-methyl-2,5-diphenyl-silacyclopentane (**10**) to derivatise alcohols.

Derivatisation experiments using the cyclic chlorosilacyclopentane **10** were some of the first conducted in this research and therefore involved some difficulties. Initially, a series of experiments was performed to derivatise dried alcohols that were present in large excess and used as the reaction solvent. Under these conditions, all the alcohols were successfully derivatised, as exemplified in Scheme 4.4.



Scheme 4.4 Derivatisation procedure for initial studies of **10** with a series of chiral and achiral alcohols

Monitoring the reaction by GC, particularly with MS detection, provided adequate evidence that the desired silyl ether products had been formed. The GC/MS chromatogram of the derivatives of ( $\pm$ )-2-butanol (Figure 4.6) was typical of that obtained from these derivatisation reactions.

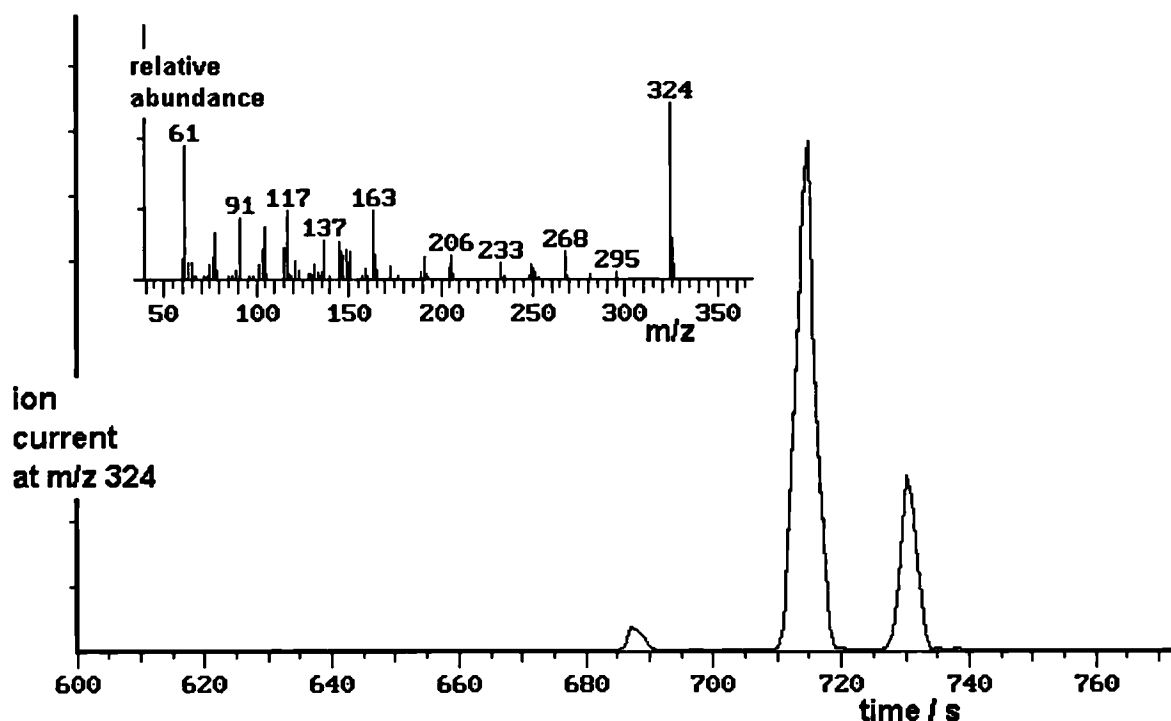


Figure 4.6 GC/MS of the derivatives of ( $\pm$ )-2-butanol and chlorosilane (10). The GC shows the typical pattern of three isomers. The mass spectrum of the major isomer is inset.

As expected, having a higher relative molecular mass, the derivative was retained on the GC column for longer than the starting materials. The derivatives of alcohols with higher mass had longer retention times. The relative molecular mass and GC retention data are summarised in Table 4.12.





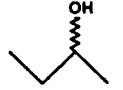
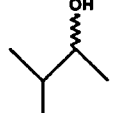

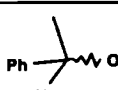
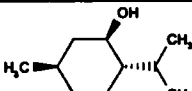
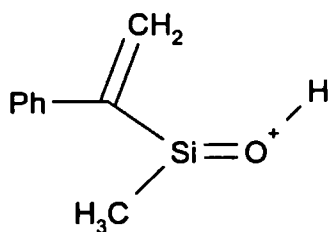
Alcohol		relative molecular mass of product	major product $t_R$ / s	ratio of product isomers (in order of elution)	product:silanol peak area ratio	boiling point of alcohol / °C
d	H <sub>2</sub> O	268	655	4:86:11	-	100
e		296	635	8:75:17	22:1	78
f		324	747	9:61:30	33:1	118
g		324	711	2:88:10	2:1	98
h		338	763	nd	4:1	112
i		366	942	nd	16:1	161
a		372	1191	3.6:81:15	2:1	204 (745mm Hg)
c		406	1337	4:72:24	6:1	-

Table 4.12 GC data for derivatives of chlorosilane (10) and alcohols

*Mass spectrometric evidence for the silyl ether products*

Considering the typical case of the derivatives of (±)-2-butanol, the mass spectra of the three components which eluted at 684, 711 and 727 s were extremely similar, having the same molecular ion ( $m/z$  324) and similar fragmentation pattern, corresponding to isomeric products.



A major fragment in all the silyl ethers, except that of ethanol, had a  $m/z$  163, which probably had the formula C<sub>9</sub>H<sub>11</sub>SiO, and the structure shown, or an isomeric form. This would be the result of the loss of the alcohol and an ethylbenzene radical.

### Chromatographic evidence for the product isomers

Peak area ratios are reported throughout in order of elution. In common with all the silyl etherifications, the three products formed from 2-butanol were present in different ratios (2:88:10) from those of the precursor silane (which was typically 12:16:72) but they were still considered to be the derivatives of the isomeric chlorosilanes. All the derivatives of alcohols gave isomer peaks in approximately the same ratio.

A peak at 655s with  $m/z$  268 in the GC/MS of **10e** was due to the molecular ion of the silanol decomposition product of **10** that had reacted with water in the starting material. This was accompanied by 2 minor peaks, corresponding to the *meso*-isomeric equivalents. The EIMS molecular ions of all the silyl ether products were stable, being the base peaks in all cases except the product formed from 1-phenylethanol.

In this earlier work where chlorosilane **10** was reacted, in the absence of base, with a large excess of the alcohol at 15°C the reaction was fairly rapid, with ca. 20% product being formed in the first 10 minutes as shown for the reaction of 2-butanol in Table 4.13.

time / minutes	10	40	90	180	1320
silyl ether product peak area	2.7	3.6	7.0	9.6	14.0

Table 4.13 GC product peak area vs. reaction time for the derivatisation of 2-butanol with chlorosilane **10**.

Four diastereoisomeric products were expected from the mixture of the four stereoisomers of the cyclic chlorosilane **10** (compare with the structures of the precursor silane shown in Scheme 3.1) and the racemic alcohol. Assuming that the reaction of the chlorosilane with the alcohol was fairly non-stereoselective, the major GC peak was believed to contain the two diastereoisomeric products that had originated from the racemic chlorosilane.

On this basis, the well-separated diastereoisomeric derivatives eluted before and after the main peak were the products of the *meso*- diastereoisomers of the chlorosilane reagent.

However, it was possible that the reaction was moderately stereoselective and that the products of the racemic chlorosilane gave rise to the second and third peaks. This was investigated by carrying out the derivatisation in a similar way, but using an achiral alcohol.

*Investigation of product stereoisomers using an achiral alcohol as reagent*

3-pentanol was selected because it was a convenient achiral secondary alcohol, which would be expected to have similar steric properties in its reaction as did menthol. The pattern of products that resulted was much like that seen with the chiral alcohols. *i.e.* three isomeric peaks were resolved. In order of elution, there was one minor peak, followed by a major peak, then a peak of intermediate size. (Figure 4.7).

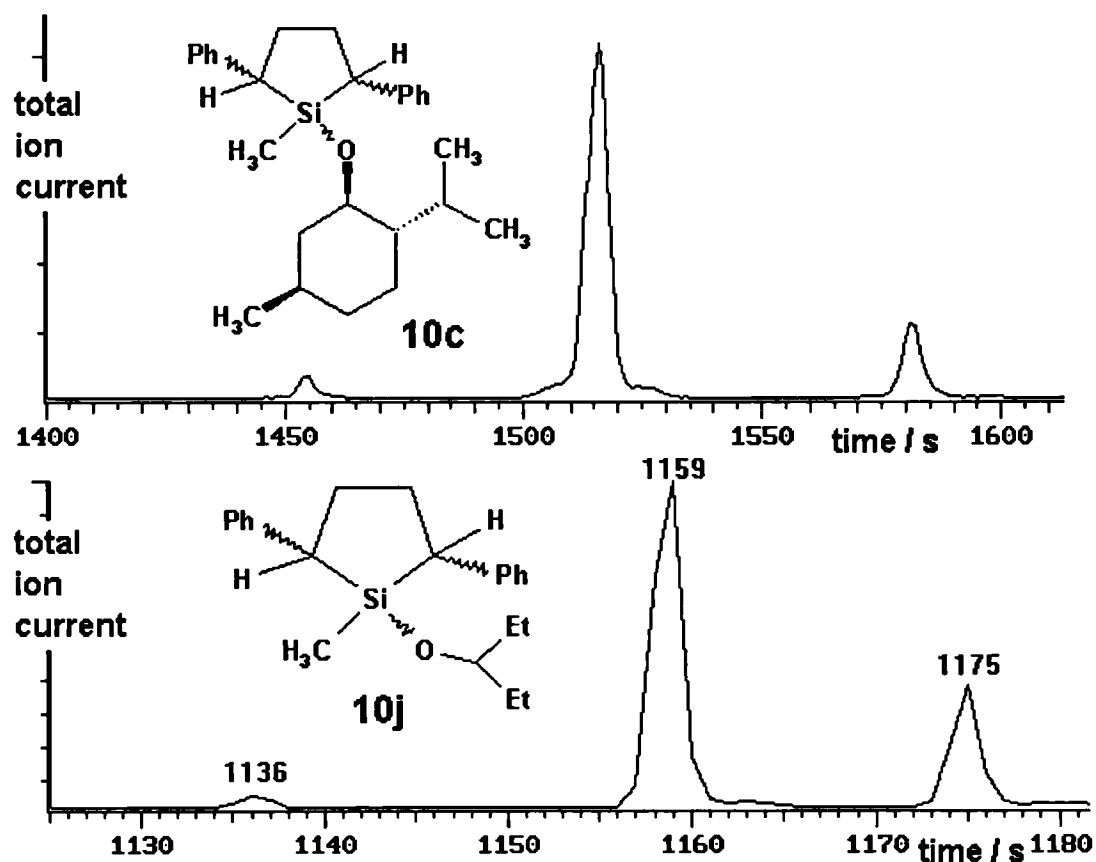


Figure 4.7 Comparison of the two gas chromatograms of the products of chlorosilane 10 and a) menthol and b) 3-pentanol.

While it had been possible that the two isomeric peaks having higher peak area may have been the diastereoisomers originated from racemic **10**, the same could not be true for **10j**, derived from 3-pentanol.

Small scale preparative HPLC was carried out on the product mixture. Fractions from the two major isomers were collected ( $t_R$  /min: 6.2 and 8.8) and analysed by GC/MS, which showed that they corresponded to the isomers eluted at 1159 s and 1175 s.  $^1\text{H}$  NMR spectra of the two isomers suggested that the 1159 s component originated from an (*E*)-isomer, having non-equivalent ethyl signals from the pentoxy fragment. The 1175 s isomer had a more simple spectrum, readily attributed to one of the higher symmetry *meso*-isomers. This was in accordance with the chemical shifts of the  $\text{SiCH}_3$  group. The 1159 s isomer had  $\delta_{\text{H}}(\text{SiCH}_3) = 0.1$  ppm, compared with the 1175 s isomer where  $\delta_{\text{H}}(\text{SiCH}_3) = -0.4$  ppm. These shifts corresponded to the 1159 s isomer being the product of the racemic chlorosilane, and the 1175 s isomer being the product of a *meso*-isomer of the chlorosilane, that with the phenyl groups adjacent to the  $\text{SiCH}_3$  group. This was taken to be evidence that the two major isomeric products were derived from geometric isomers of chlorosilane **10**. The minor (first-eluted) isomer was therefore believed to be the other geometric isomer.

#### *Experiments using purified racemic chlorosilane*

A further experiment was conducted using 3-pentanol and racemic chlorosilane **10**, which had a negligible *meso*- isomer content (the chlorosilane was prepared from racemic 1-methyl-2,5-diphenylsilacyclopentane (**7**), chromatographically purified as described in Section 3.1.2). The products of this reaction eluted as a single peak in the HPLC, with a retention time corresponding to the second of the three isomeric peaks (*i.e.* as the 1159 s component in Figure 4.7). NMR of the product corresponded to that of the 1159 s component isolated by small-scale preparative chromatography from the earlier experiment

with the mixed isomers of **10**. The NMR again showed that the products originated from an (*E*)-isomer, having non-equivalent ethyl signals from the pentoxy fragment.

*Reaction of alcohols with chlorosilane 10 with and without base*

As described above, earlier reactions with a large excess of alcohol proceeded at an acceptable rate (Table 4.13). Later reactions with 2-butanol were carried out with stoichiometric proportions of reagents in deuteriochloroform, with pyridine added to increase the rate. The reaction of 2-butanol (dried over activated grade 4A molecular sieve) with **10** in deuteriochloroform solution, before the addition of pyridine was extremely slow (less than 10% product after 4 days at 50°C). This was in marked contrast to the reaction described above. Two main differences existed between the procedures; in the earlier work the alcohol was dried by reflux from magnesium, which was less effective for 2-butanol (b.p. 98°C) than for the higher-boiling alcohols, and the alcohol was used in large excess. Addition of pyridine to the unreacted mixture of alcohol and **10** caused the reaction to proceed to completion after a further 15 hours at 20°C.

The addition of pyridine also increased the rate of reaction of **10** with 3-pentanol, 1-phenylethanol, 2-octanol and menthol.

*NMR evidence for the diastereoisomeric products prepared from purified chiral chlorosilane 10 with racemic 2-butanol.*

The NMR of silyl ethers prepared from purified racemic chlorosilane was greatly simplified. The diastereoisomeric <sup>1</sup>H signals, particularly in the alcohol residue, were easily distinguished, as shown in Figure 4.8.

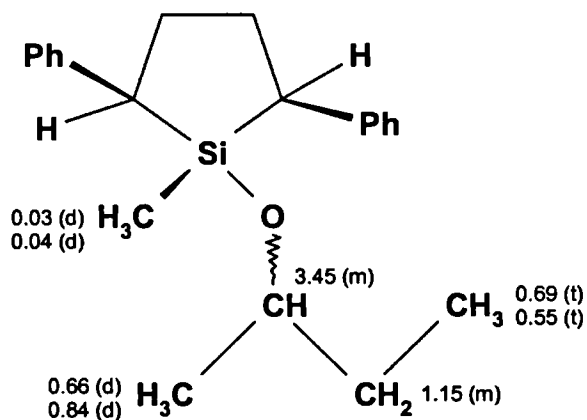


Figure 4.8 Chemical shifts of the diastereoisomers of **10g**

*Differences in the rate of reaction of the chiral and the meso-isomers of chlorosilane 10.*

A number of reactions of chlorosilane **10** and alcohols that were carried out in deuteriochloroform solution in the absence of base were monitored frequently, mostly by GC/MS. In this way, for a particular alcohol, the rate of its reaction with each of the three geometric isomers of chlorosilane **10** could be compared. In most cases there was little discrimination. However, it was quite evident that the more hindered alcohols reacted with the geometric isomers of the chlorosilane at different rates.

Under these conditions, the rates of reaction were slow, the reactions often not being followed to completion. The quantification of the earliest-eluting product (always the minor isomer) was less reliable than that of the later-eluting products because it was present at a lower concentration.

The reaction of menthol with **10** was followed in several similar experiments, always showing this stereochemical bias. Two representative examples are given in Tables 4.14 and 4.15.

Reaction time / days	Relative concentration of product isomers		
	First-eluted peak	Second-eluted peak	Third eluted peak
1	4	80	16
2	5	75	20
8	4	64	32
22	4	67	30

Table 4.14 Ratio of product isomers formed in the reaction of menthol and the mixed isomers of chlorosilane **10**.

The evidence from these studies showed that the third-eluted product was formed more slowly than the major product with intermediate retention time. Following the relationships proposed above, this indicates that the chiral chlorosilane reacted faster with the alcohol than did the *meso*-chlorosilane isomer which gave rise to the longest retained product.

In only one experiment were very early samples taken. Menthol was used in a threefold excess, but it is believed that the main reason for the interesting result was simply that the mixture was sampled early.

Reaction time	Relative concentration of product isomers		
	First-eluted peak	Second-eluted peak	Third eluted peak
1 hour	7	89	4
2.5 hours	6	89	4
4 hours	5	90	5
4 days	5	68	27

Table 4.15 Ratio of product isomers formed in the reaction of menthol and the mixed isomers of chlorosilane **10** - further study with early sampling.

The same trend in product isomer ratio was observed in the reaction of 3-pentanol with the mixed isomers of chlorosilane **10** as shown in Table 4.16.

Reaction time	Relative concentration of product isomers		
	First-eluted peak	Second-eluted peak	Third eluted peak
1 hour	4	80	16
4 hours	3	78	19
7 days	3	59	38
... + 18h @ 70°C	5	67	28

Table 4.16 Ratio of product isomers formed in the reaction of 3-pentanol and the mixed isomers of chlorosilane **10**.

Many of these reactions were also monitored by  $^1\text{H}$  NMR. In the reaction of **10** with 3-pentanol, the  $\text{SiCH}_3$  signal of the enantiomers was shifted by -0.25 ppm as the chlorine was substituted by  $\text{OCH}(\text{CH}_2\text{CH}_3)_2$ . The analogous shift in signal of the *meso*-isomer having the more shielded  $\text{SiCH}_3$  was also -0.25 ppm. While it was probable that the shift was similar in the other *meso*-isomer, it was not possible to reliably identify the  $\text{SiCH}_3$  signal of the product of this isomer because it was less intense and, being less shielded, was more easily lost among impurity and by-product signals.

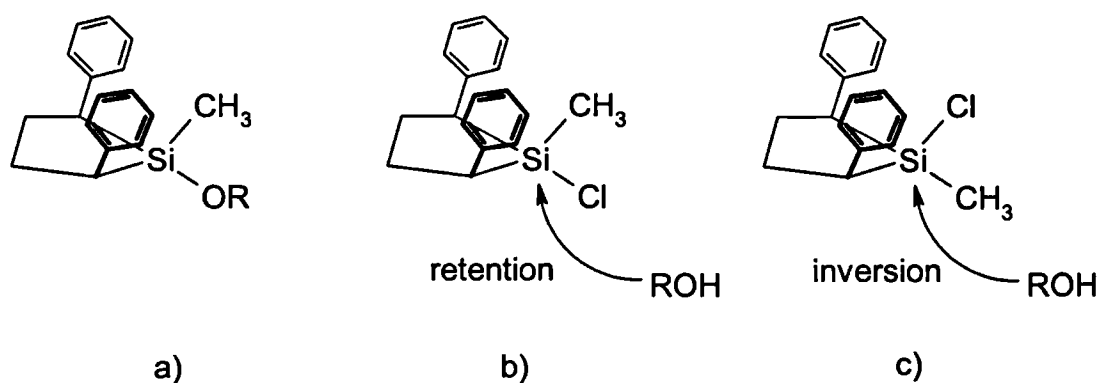
Therefore, while NMR evidence correlated with the GC/MS data for the two later-eluted product isomers from reactions of **10** with any of the alcohols, it was often impossible to obtain quantitative NMR data for the first-eluted isomer.

Nevertheless, it was possible to approximate from the  $^1\text{H}$  NMR that the ratio of the product isomers was similar to that of the chlorosilane isomers. The simplest example was in the preparation of **10j** (3-pentanol / **10** reaction). Here, in order of increasing shielding, the chlorosilane isomers were in the ratio 6:74:20 (NMR data), while the product isomers were in the ratio 5:67:28 (GC/MS data). (The correlation between the NMR and GC/MS data was noted earlier in this section, where the product isomer that eluted last was shown to be that with the most-shielded  $\text{SiCH}_3$  group. The product of the enantiomers of **10** had intermediate shift, while the first-eluted products had the least-shielded  $\text{SiCH}_3$  group).



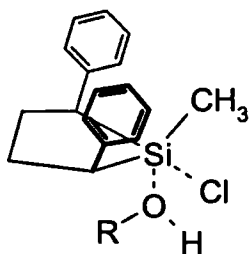
All the diastereoisomeric silyl ether products of **10** eluted as three peaks, with similarly good resolution. Thus it was believed that the elution order probably reflected the stereochemistry in each case.

In summary, geometric isomer (a) in Scheme 4.5 was formed most slowly. This was formed from one of the *meso*-chlorosilane isomers (b) or (c) in Scheme 4.5 by either retention or inversion of configuration at silicon, respectively.



Scheme 4.5 The slowest-formed geometric isomer (a) and the two possible mechanisms that would give rise to that product.

On steric grounds it appears from Scheme 4.5 that either mechanism of substitution to produce *meso*-isomer (a) is favoured (compared with the enantiomers), so it is not clear why this isomer was formed more slowly than the enantiomers.



If the assumptions made above are correct, a possible explanation for the slowness of reaction to give this isomeric product might be that a five-membered intermediate is involved. The intermediate to this product may be more easily formed, but may also be more stable than that derived from the enantiomers of **10**.

Note that a similar study was not conducted to investigate the relative rates of reaction of the isomers of **10** in the presence of base.

*Attempt to prepare the derivative of 10 and  $\alpha$ -methyl-2-naphthalenemethanol*

In an attempt to increase the difference between the diastereoisomeric derivatives, the naphthalene analogue of 1-phenylethanol, *i.e.*  $\alpha$ -methyl-2-naphthalenemethanol, was subjected to the derivatisation procedure. In this earlier work, the alcohols used were all liquids and were used in large excess as reaction solvents. Under these conditions, reaction rates were acceptable (reactions monitored by GC/MS and often not followed to completion) so no base was added.  $\alpha$ -Methyl-2-naphthalenemethanol (a solid, used in large excess) was dissolved in two drops of ethyl acetate (because it was a convenient dried solvent) to allow homogeneous reaction. There was no evidence for the analogous silyl ether in the GC/MS of the  $\alpha$ -methyl-2-naphthalenemethanol / **10** reaction mixture (no molecular ion or expected fragment with  $m/z$  163 (the base peak in the 1-phenylethanol derivative, **10a**) was seen in the GC). However, two equally-sized product peaks appeared which eluted late in the chromatogram and had indistinguishable mass spectra (Figure 4.9).

These components, having the same mass spectra and being present in equal amounts, appeared to be diastereoisomeric. It was unlikely that the silyl ether of the  $\alpha$ -methyl-2-naphthalenemethanol would behave very differently in the mass spectrometer from that of the phenylethanol, so it appeared that some other diastereoisomeric products had been formed. Although these compounds were not the intended products, their identity was considered worth investigating, partly because of their ease of separation on the GC column, and also because they may have arisen from a side reaction that might occur in future work.

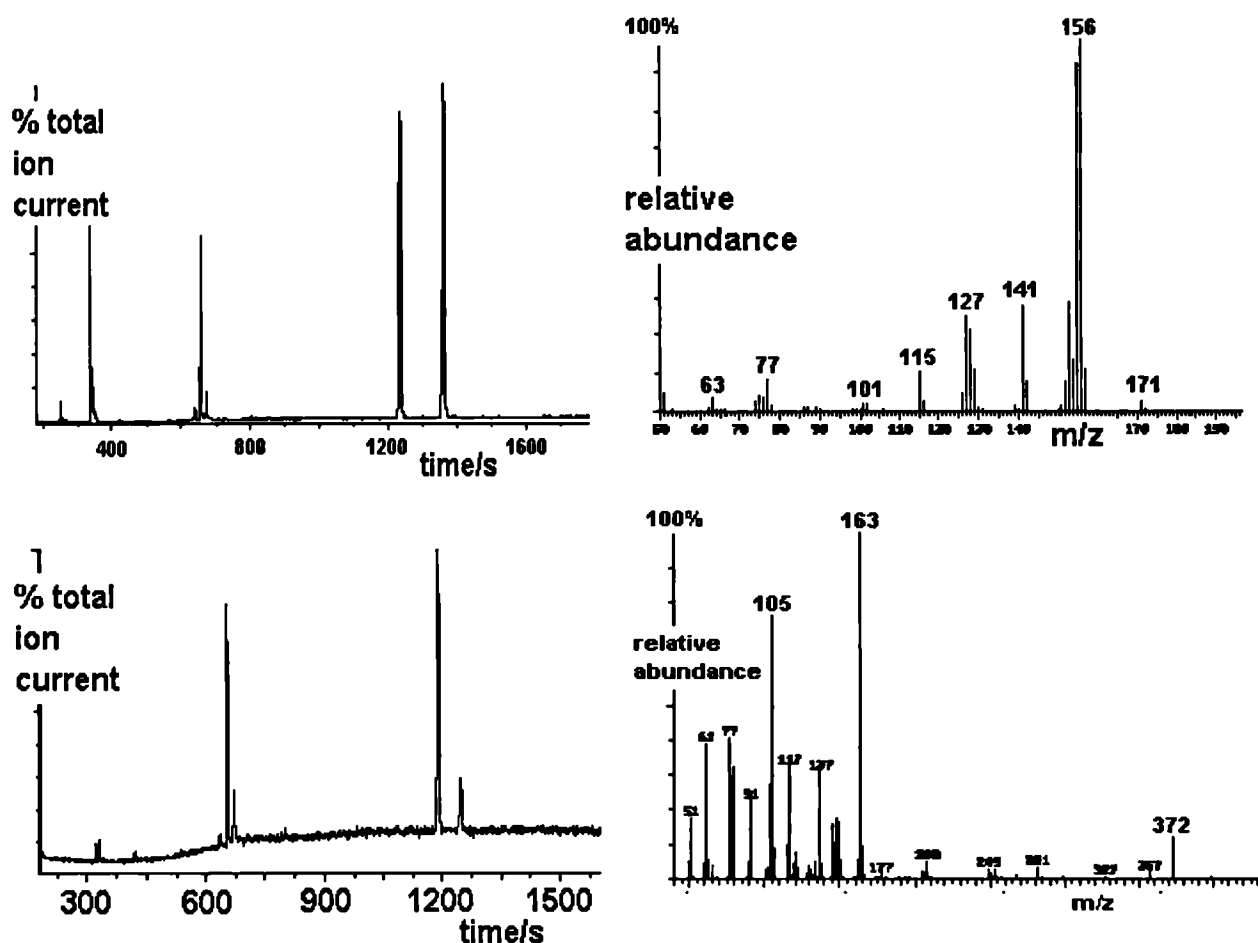


Figure 4.9 Gas chromatograms and mass spectra of the products of reaction of the chlorosilane **10** and  $\alpha$ -aryl alcohols.

Above: GC of the  $\alpha$ -methyl-2-naphthalenemethanol derivatives and mass spectrum of either major component.

Below: GC of the 1-phenylethanol derivative (**10a**) and mass spectrum of major component.

The mass spectrum of the  $\alpha$ -methyl-2-naphthalenemethanol product was much like that expected for 2-naphthaldehyde, which has a major ion at  $m/z$  156 for  $[C_{11}H_8O]^+$ . It was not likely that the two product peaks were the isomeric 1- and 2-naphthaldehydes, because the retention times were too long, so the  $m/z$  156 ions were thought to be fragment ions, rather than molecular ions.

In an attempt to observe the molecular ion, the GC/CIMS spectrum was recorded, using *iso*-butane as reagent, but the largest significant ion was still at  $m/z$  156.

A similar silyl ether to the intended  $\alpha$ -methyl-2-naphthalenemethanol product was prepared by forming the TMS derivative with N,O-bis(trimethylsilyl)-trifluoroacetamide (BSTFA). The product so formed gave a weak (6%) molecular ion, with a base peak at  $m/z$  229, being the  $[M-15]^+$  ion (loss of methyl radical) and no significant  $m/z$  156 ion. This behaviour, which was quite predictable, provided further evidence that the diastereoisomeric products under investigation were not silyl ethers analogous to the series of alcohol derivatives.

The products of the reaction of **10** and  $\alpha$ -methyl-2-naphthalenemethanol appeared not to be silyl ethers as they were not decomposed by reaction with tetrabutylammonium fluoride (which would cleave a silicon-oxygen bond). These products were also not formed simply by heating the  $\alpha$ -methyl-2-naphthalenemethanol, either in the presence or in the absence of ethyl acetate.

To obtain NMR spectral information on these compounds, the product mixture was fractionated by preparative HPLC.  $^1\text{H}$  NMR spectra of these components were very similar, appearing to confirm the presence of a  $\text{C}_{10}\text{H}_7\text{CH}(\text{CH}_3)-$  group. These compounds could not have been the starting material ( $\text{C}_{10}\text{H}_7\text{CH}(\text{CH}_3)\text{OH}$ ) because their retention times were far longer and they seemed to be diastereoisomeric (equally-sized GC peaks and indistinguishable mass spectra).

A structure that would fit the NMR evidence was the dimeric ether of the alcohol,  $\text{C}_{10}\text{H}_7\text{CH}(\text{CH}_3)\text{OCH}(\text{CH}_3)\text{C}_{10}\text{H}_7$  (**13**). The CH quartet was shifted upfield relative to that of the alcohol (4.74 *cpw* 5.01 ppm), consistent with the product being an ether. Since the product is formed from two molecules of a racemate, this compound could be formed as two diastereoisomers in equal amounts (unless the reaction were stereoselective), and would be capable of GC or HPLC resolution on an achiral stationary phase. Although a mass spectrum of this dimer was not available in the RSC Eight Peak Index of Mass

Spectra, the analogous benzyl alcohol ether,  $(\text{C}_6\text{H}_5\text{CH}_2)_2\text{O}$  was listed as giving no molecular ion.

The unexpected product of the reaction between  $\alpha$ -methyl-2-naphthalenemethanol and **10** was therefore believed to have the structure shown in Figure 4.10. In order to confirm this, a sample of **13** was obtained from a commercial source. This had the same retention times and EIMS and therefore confirmed the suspected structure.

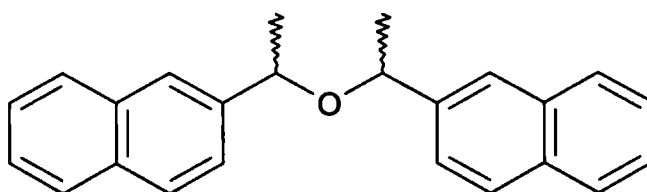


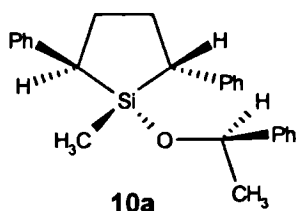
Figure 4.10 Proposed structure (**13**) of the unexpected diastereoisomeric derivatives of  $\alpha$ -methyl-2-naphthalenemethanol

The difference between the products of the reaction of **10** with 1-phenylethanol and  $\alpha$ -methyl-2-naphthalenemethanol may have been due to the need to use a solvent (ethyl acetate) for the reaction of the latter (solid) alcohol. A single reaction of **10** with  $\alpha$ -methyl-2-naphthalenemethanol was carried out in much the same way, but with dry acetonitrile as solvent, but on this occasion neither silyl ether nor dialkyl ether was apparent in the GC/MS.

Subsequent reactions with other chlorosilanes and alcohols were catalysed with base. It would seem likely that this reaction would also have been successful had a base been present.

Being a departure from the main objectives of this project, this reaction was not investigated further.

**4.1.14**      *Further study of 10a, 10b and 10c, the diastereoisomeric ethers of 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10)*  
*i) 1-methyl-2,5-diphenylsilacyclopentyl-1-(1-phenethyl)ether (10a)*



As with the reaction of the cyclic chlorosilane **10** with any of the chiral alcohols, four diastereoisomeric products were expected to be present in the preparation of **10a**. Gas chromatography readily separated these diastereoisomers as three peaks. The most obvious explanation was that the two minor peaks represented the two ether isomers that originated from the two *meso*- chlorosilane isomers, while the major peak was due to the ether from the racemic chlorosilane.

The 1-phenylethanol derivatives of the isomers of the cyclic chlorosilane (**10a**) were resolved as three peaks by HPLC. They followed a pattern of relative intensity that resembled that of the precursor chlorosilane. Fractions containing the product diastereoisomers were collected from the HPLC column. The elution order was the same from both the HPLC and the GC. Thus the HPLC fraction with intermediate retention time had the largest peak area and, when analysed by GC/MS, appeared as one peak having the same retention time as the major peak in the GC of the mixture. This HPLC fraction was shown by  $^1\text{H}$  NMR to contain two diastereoisomers in equal amounts. The chemical shifts of protons in analogous positions were very similar for the two diastereoisomers. This evidence, together with the relative intensities of the isomers, suggested that the two diastereoisomers that originated from racemic **10** were unresolved by HPLC. GC/MS of this fraction showed that these diastereoisomers were also unresolved by GC under the stated conditions.

*Preparation of 1-methyl-2,5-diphenylsilacyclopentyl 1-(1-phenethyl) ether (10a) using stoichiometric proportions of reagents*

As described above, the silyl ether was readily formed from chlorosilane 10 and 1-phenylethanol when the latter was present in large excess, being used as the reaction solvent. However, in a later series of experiments, this reaction was repeated using neat reagents in stoichiometric proportions. The GC/MS was recorded as shown in Figure 4.11.

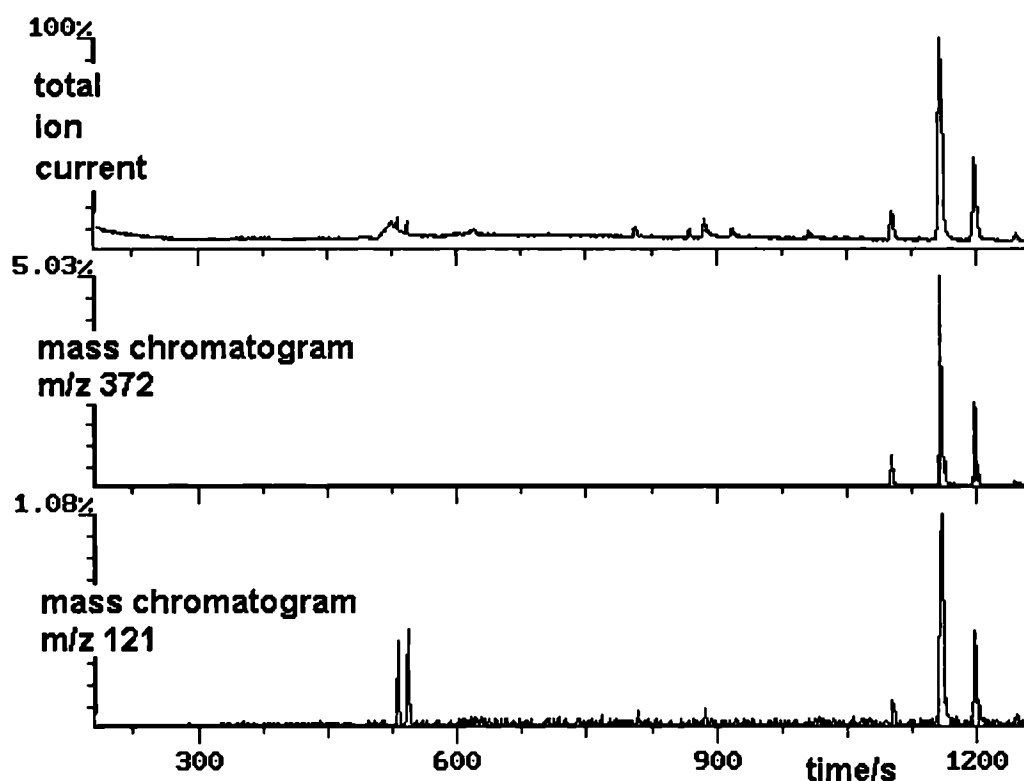
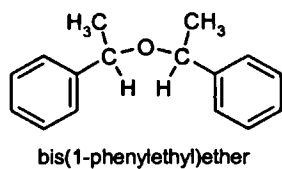


Figure 4.11 GC/MS of the products of reaction of chlorosilane 10 and 1-phenylethanol  
GC temperature programme: 90→250 °C at 10 °C min<sup>-1</sup>.

The mass chromatogram displayed for m/z 372 shows the three silyl ether (10a) product peaks (assumed to contain four isomers in total). The mass chromatogram displayed for



m/z 121 shows two product peaks at 531 and 543 seconds, having indistinguishable mass spectra with no molecular ion. For similar reasons to those used to deduce the structure of 13, these

compounds were believed to be the diastereoisomers of bis(1-phenylethyl)ether.

A commercial sample of bis(1-phenylethyl)ether was obtained and the GC/MS recorded.

The two diastereoisomers eluted with the same retention times and mass spectra as the two

by-products from the reaction of **10** and ( $\pm$ )-1-phenylethanol. In this case, the initial GC temperature was reduced to 60°C and the diastereoisomers eluted at 708 and 720 seconds (Figure 4.12).

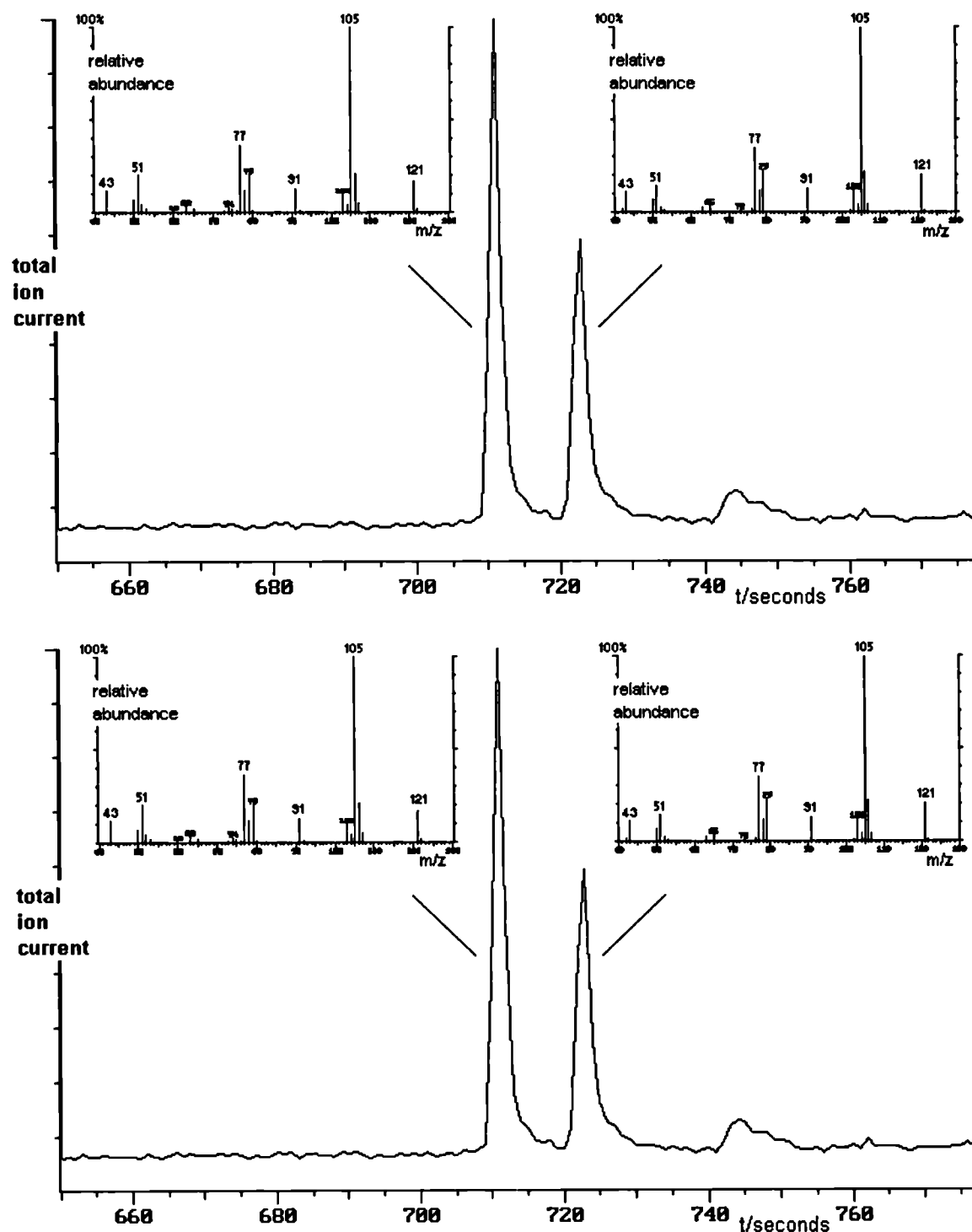


Figure 4.12 Comparison of GC/MS results from the diastereoisomers of (above) bis(1-phenylethyl)ether and (below) the by-products of the reaction of **10** and ( $\pm$ )-1-phenylethanol

*GC temperature programme: 90→250°C at 10°C min<sup>-1</sup>.*



In this experiment, an NMR spectrum of the total reaction mixture was recorded which showed that the silyl ether was not the major product. The  $\text{CH}_3\text{CH}-$  group of the major product had chemical shifts ( $\delta_{\text{H}}$ : 1.8 (3 H, d,  $\text{CH}_3$ ), 5.1 (1 H, q, CH)).

It was also apparent from the GC recorded at the lower initial temperature ( $60^\circ\text{C}$  compared with  $90^\circ\text{C}$ ), that the major product (large peak eluted at 283 s, shown in Figure 4.13) had not been previously detected in the GC/MS analysis of the reaction mixture. (At the higher initial temperature this component would have been undetected, eluting within the first 180 s of the chromatogram when the MS filament was switched off). This compound had a molecular ion at  $m/z$  140, with a  $[\text{M}+2]^+$  molecular ion having 30% RA, corresponding to a compound containing one chlorine atom. An INCOS spectral library search located an exact match with 1-chlorophenylethane. This was clearly the major product of this reaction and was in accord with the findings from the  $^1\text{H}$  NMR spectrum.

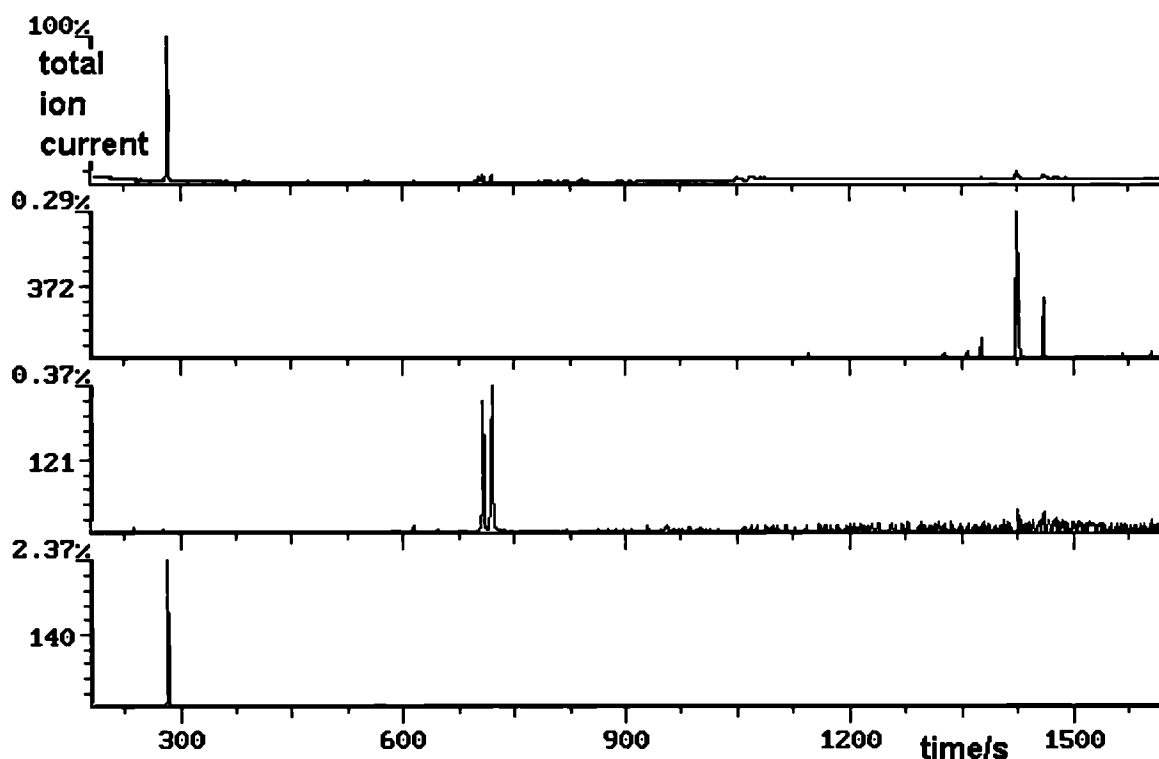


Figure 4.13 GC/MS of the products of reaction of chlorosilane 10 and 1-phenylethanol  
GC temperature programme:  $60 \rightarrow 250^\circ\text{C}$  @  $10^\circ\text{C min}^{-1}$ .

Two other experiments were conducted which were relevant to the study of the reactions with 1-phenylethanol. In one case, in a brief investigation into the possibility of chlorinating the silane **7** in the presence of alcohol to give a one-pot preparation of the silyl ether **10a** *via* the chlorosilane **10**, chlorine was bubbled through neat 1-phenylethanol. The  $^1\text{H}$  NMR was consistent with the major product being 1-chlorophenylethane and with some bis(1-phenylethyl)ether being formed.

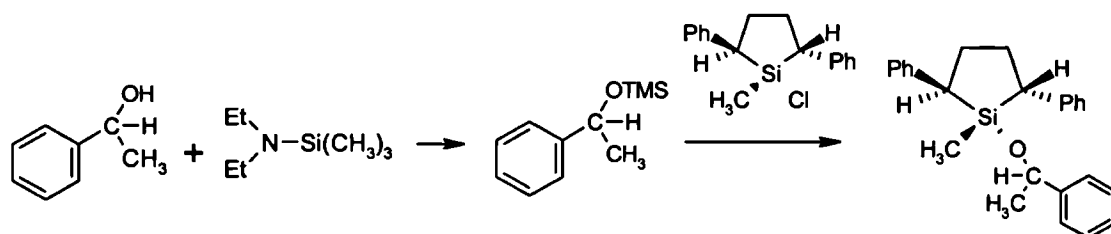
Another experiment was designed to prepare the TMS ether of 1-phenylethanol (prior to transsilylation with **10** as a route to **10a**). Two equivalents of chlorotrimethylsilane were added to neat 1-phenylethanol. After stirring for 20 h, a small volume of immiscible lower layer had formed, which was insoluble in  $\text{CDCl}_3$ . The upper layer was evaporated with  $\text{N}_2$  and analysed.  $^1\text{H}$  NMR showed that the major product was 1-chlorophenylethane and that a little bis(1-phenylethyl)ether was also formed. Evidence for both compounds was also obtained from the GC/MS and from the  $^1\text{H}$  NMR spectra.

From the work described above, it was evident that the major reaction of chlorosilanes with benzylic alcohols would be the substitution of the alcohol by chlorine.

#### *Derivatisations with TMS ether of the alcohol*

An alternative route to **10a** was successful *via* the TMS ether of 1-phenylethanol, prepared by reaction with N,N-diethylaminetrimethylsilane. Transsilylation of the TMS ether with ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane gave the required product in good yield as shown in Scheme 4.6. An interesting feature of this reaction was that the product isomer ratio was biased with respect to the results obtained from **10** with any of the underivatised alcohols. In the case of the reaction with the TMS ether of 1-phenylethanol, the later-eluted (third) product isomer was formed more rapidly than the others. After a short period of time, the second and third peaks had similar areas, while the first diastereoisomer peak remained below the limit of detection. This was in contrast to the

findings of, for instance, the reaction with 3-pentanol, where the most-slowly formed product was the *meso*- product in which the SiCH<sub>3</sub> group was more shielded by the phenyl groups. Thus it may have been that the bulkier group in the -OTMS substrate induced the reaction to proceed with an alternative mechanism (inversion rather than retention or *vice-versa*).



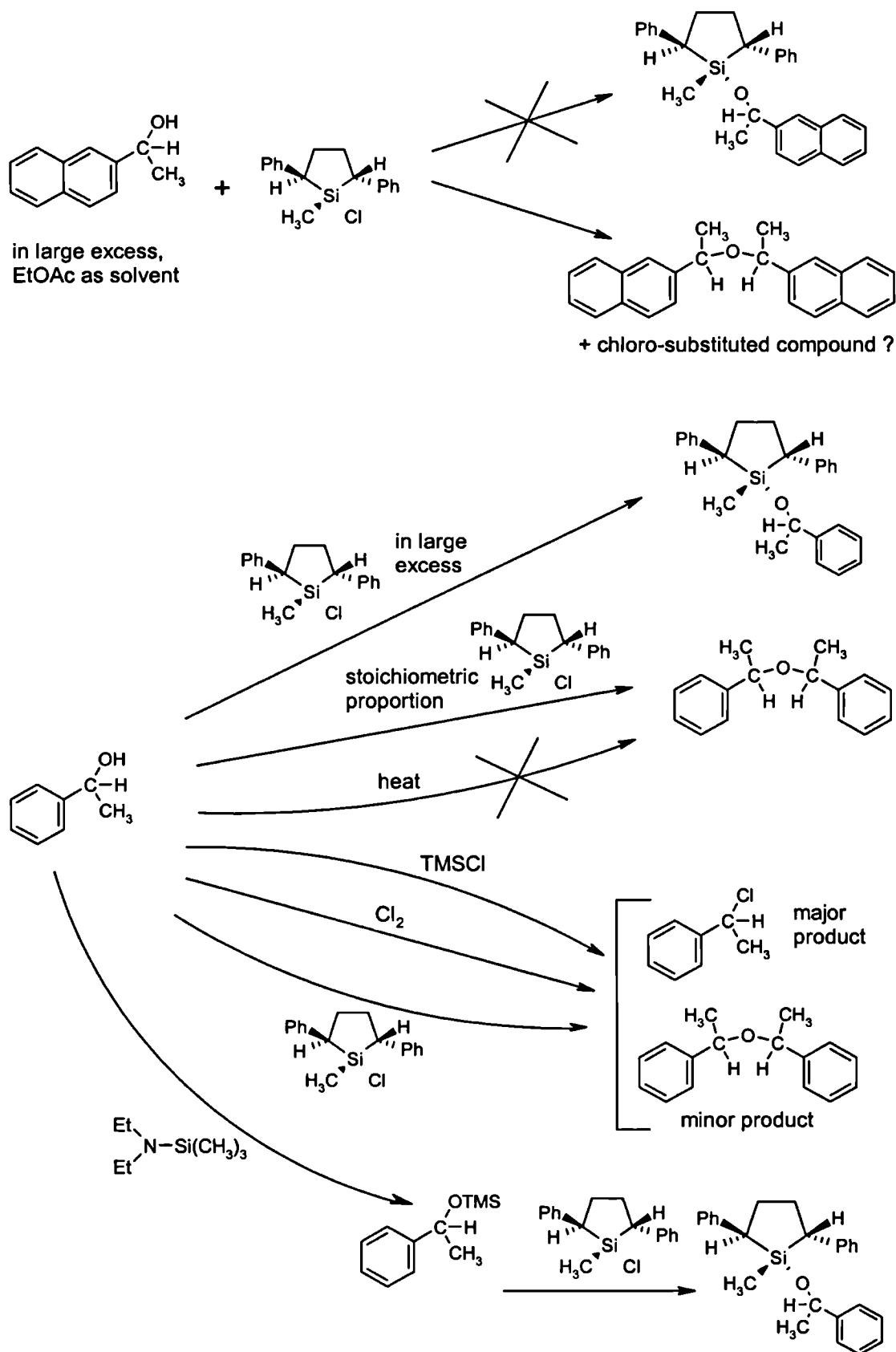
Scheme 4.6 Preparation of **10a** via transsilylation.

A similar experiment was carried out with the TMS ether of the related secondary alcohol, ( $\pm$ )-1-methyl-2-phenylethanol. The TMS ether was equally easily prepared and derivatised with chlorosilane **10**. As with the benzylic ether, the transsilylation reaction had a half-life of approximately 24 h.

A similar experiment was performed with ( $\pm$ )-1-methyl-2-phenylethanol without prior derivatisation with N,N-diethylaminotrimethylsilane. This alcohol was not expected to be prone to substitution by chlorine, as was 1-phenylethanol. The reaction was slower, with a half-life of *ca.* 20 days.

The GC/MS showed two major product peaks that appeared as in the latter experiment, with similar retention times and mass spectra.

The work on benzylic alcohols is summarised in Scheme 4.7.



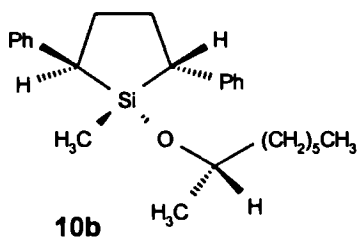
Scheme 4.7 Summary of the reactions of benzylic alcohols.

### *Significance of the chlorobenzyl product*

1-chlorophenylethane was originally not recognised as being the major product from the original reactions with 1-phenylethanol because it was not seen in the GC analysis, the temperature programme of which was designed to monitor lower volatility products. It seems to be likely that the symmetric bis(1-phenylethyl)ether shown in Scheme 4.7 may have been formed *via* 1-chlorophenylethane as intermediate.

For the same reason, a similar situation could have arisen in the reaction of **10** with ( $\pm$ )- $\alpha$ -methyl-2-naphthalenemethanol. The symmetric ether **13** may have only been a minor product. (This work was not repeated after the above explanation was proposed).

#### *ii) 1-methyl-2,5-diphenylsilacyclopentyl-1-(2-octyl) ether (10b)*



The reaction of chromatographically purified racemic 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**) with the homochiral alcohol, (S)-(+)-2-octanol was carried out. The <sup>1</sup>H NMR spectrum showed that two diastereoisomeric products

had been formed, in equal proportions, confirming the absence of stereoselectivity in the reaction of the alcohol with either enantiomer of the chlorosilane. (As previously stated, even the reactions of the two racemates confirm the absence of stereoselectivity; for instance, if the (R)-reagent reacts preferentially with the (R)-substrate, then the same will be true of the (S)- analogues, so that the (R,R)- and (S,S)-products will be formed to equal extents, and more than the formation of the (R,S)- and (S,R)-analogues). The diastereoisomers of **10b** coeluted as one peak in the GC.

Partial resolution of the diastereoisomers of **10b** was obtained by normal-phase HPLC, with separation factor  $\alpha = 1.06$  (Figure 4.14). The resolution was insufficient to allow measurement of resolution factor. Fractions from the two components were collected and analysed by GC/MS, which confirmed that they were the diastereoisomeric products,

having the same GC  $t_R$  and EIMS as had been determined from the reaction mixture. There was a slight difference between the  $t_R$  values from the two components, being 620 and 622 s. However, the peak width at half height was 4 s, explaining the lack of resolution by GC of the mixture.

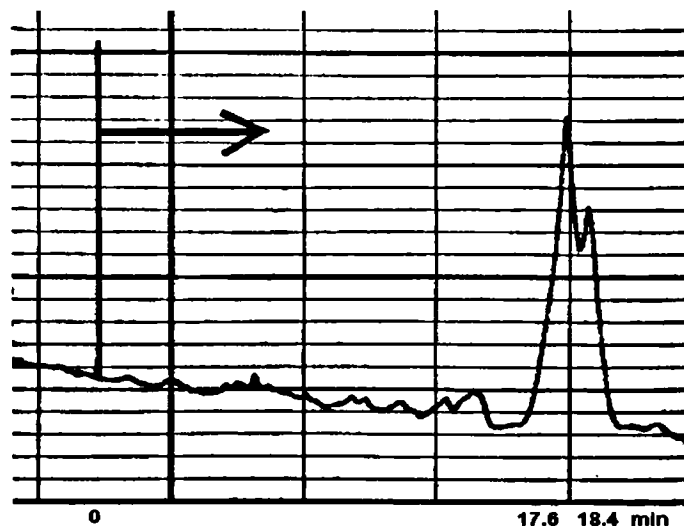
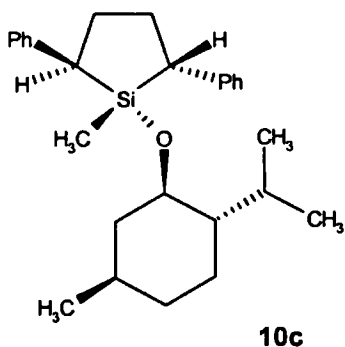


Figure 4.14 Partial separation of two diastereoisomers of **10b** by normal-phase HPLC.

iii) *1-methyl-2,5-diphenylsilacyclopentyl-1-menthyl ether (10c)*



*HPLC resolution of the diastereoisomers of 10c*

The reaction mixture of **10c** diastereoisomers (prepared from chromatographically purified racemic **10**) was injected onto a normal-phase silica column with a mobile phase of  $\text{CH}_2\text{Cl}_2$  / *n*-hexane (5.0 % v/v), separating two components, having  $t_R$ /min: 15.4 and 17.0,  $\alpha = 1.24$ ,  $R_s = 1.34$  as shown in Figure 4.15.

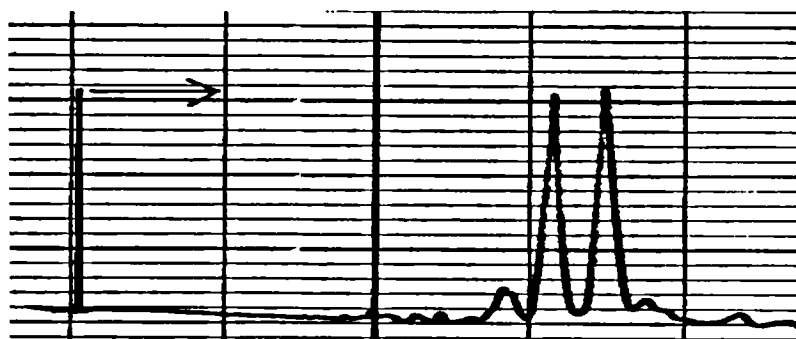


Figure 4.15 Normal-phase HPLC separation of two diastereoisomers of **10c**.

The two HPLC fractions were analysed by GC/MS, the major components having the same GC retention time (1500 and 1499 s) and the same mass spectrum as had been determined in the product mixture.

*<sup>1</sup>H and <sup>13</sup>C NMR of the diastereoisomers of 10c*

The <sup>1</sup>H NMR spectra of the two diastereoisomers were significantly different from each other and are compared with the spectrum of menthol in Figure 4.16.

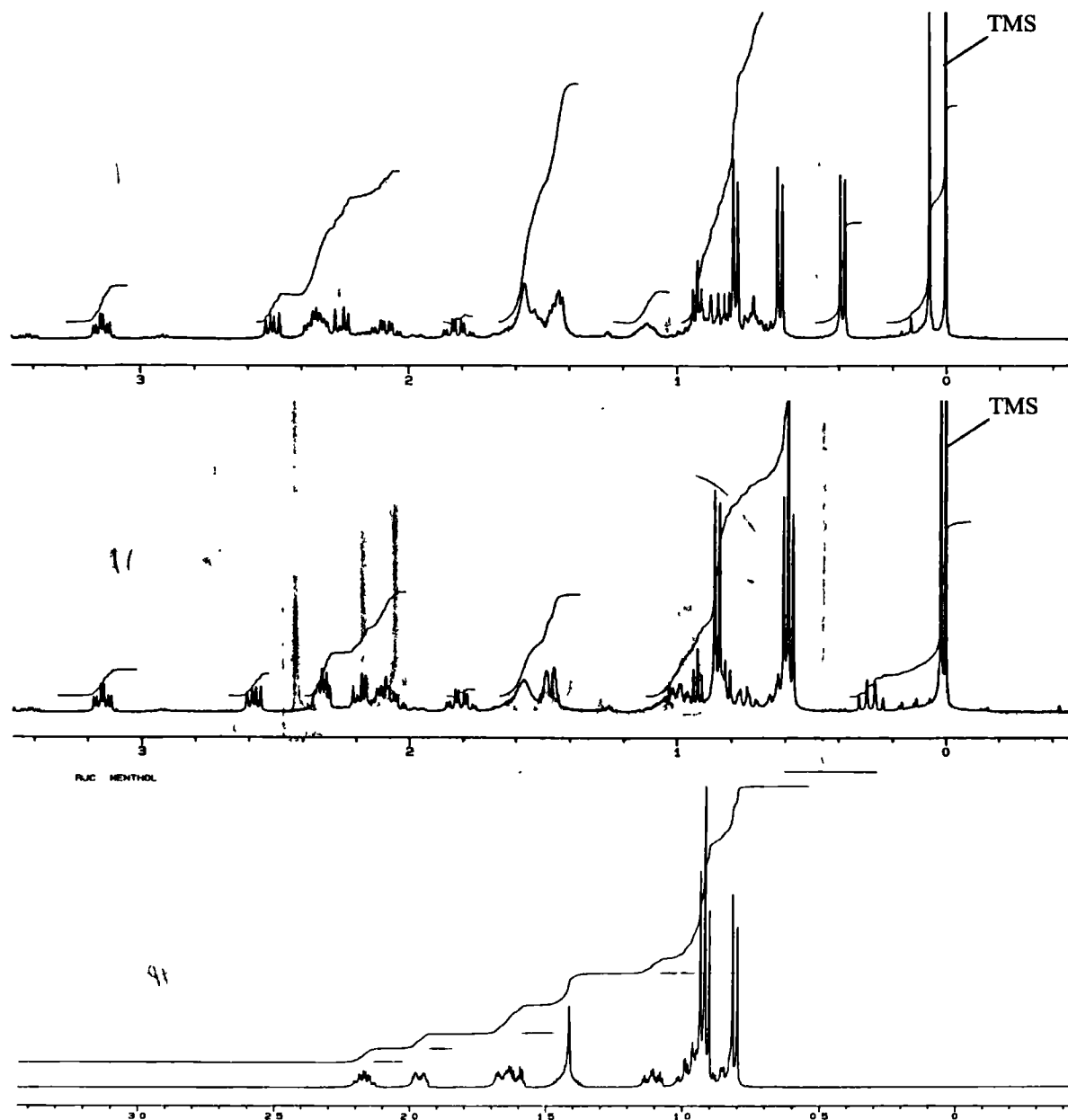
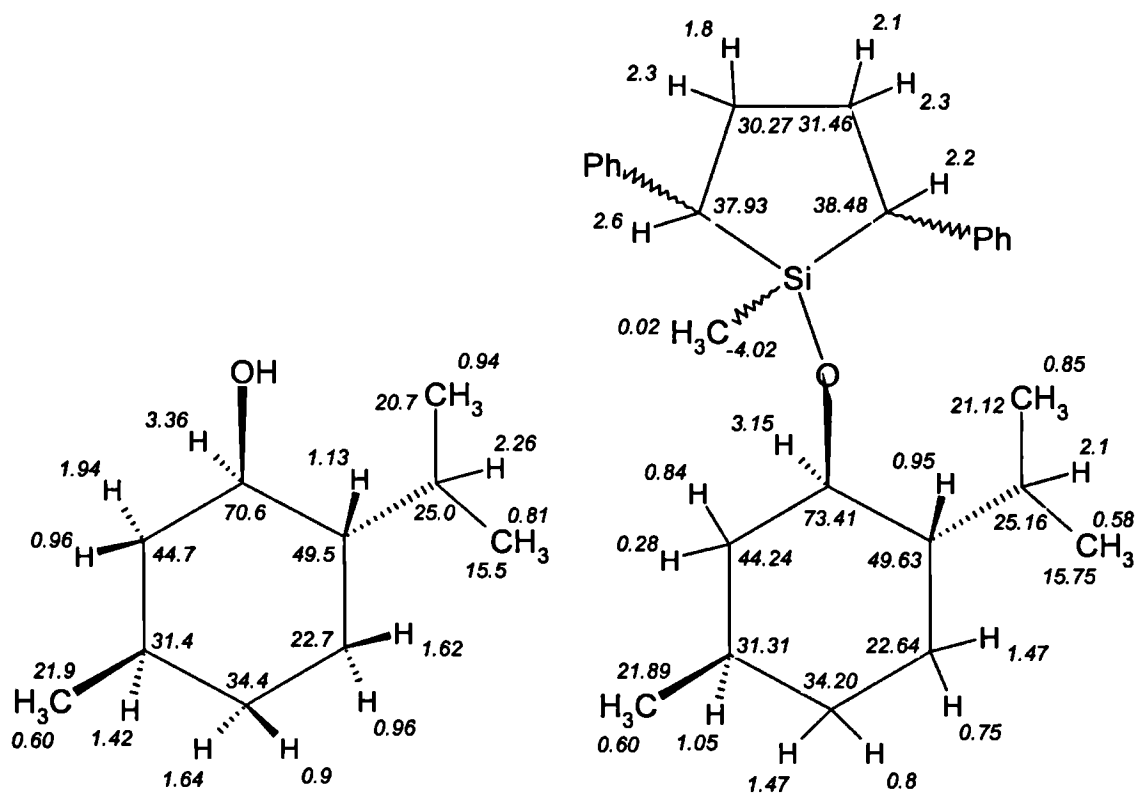


Figure 4.16 Comparison of the <sup>1</sup>H NMR spectra of the resolved diastereoisomers of 10c with that of menthol. Top spectrum: first-eluted diastereoisomer; middle spectrum: second-eluted diastereoisomer; lower spectrum: menthol.

The  $^{13}\text{C}$  shifts of the menthol moiety were hardly affected by derivatisation, so could easily be used as a basis for the assignment of the derivatives, with reference to published data for menthol, particularly those reported by Turner<sup>182</sup> which included both carbon and proton correlations. The  $^1\text{H}$ - $^{13}\text{C}$  COSY and  $^1\text{H}$  NMR spectra were used to assign the signals from the later-eluted diastereoisomer of **10c**, as shown in Scheme 4.8. All the proton assignments were in accord with the  $^{13}\text{C}$ - $^1\text{H}$  COSY spectrum, with the exception of the protons adjacent to the carbon atoms with  $\delta_{\text{C}}$  34.20 and 22.64 ppm (both  $\text{CH}_2$  according to the DEPT spectrum). The only observed couplings with these carbon atoms were to two protons within the two bands between 1.46-1.48 ppm. It is possible that these couplings may have been seen if the NMR experiment had been repeated at greater sensitivity. However, the  $^1\text{H}$ - $^1\text{H}$  COSY spectrum showed that these protons were coupled to (among others) protons at *ca.* 0.8 and 0.75 ppm, so these protons have been assigned as in Scheme 4.8. The  $^1\text{H}$ - $^1\text{H}$  COSY spectrum was too complex to allow simple interpretation of the integrals and the couplings without reference to the  $^{13}\text{C}$ - $^1\text{H}$  spectrum.

Unfortunately, although the chromatographic fractionation of the first-eluted diastereoisomer of **10c** was repeated on a number of occasions with comparable results, only small amounts of the product were collected, which were never completely pure. As a consequence, the  $^{13}\text{C}$  and the  $^1\text{H}$ - $^{13}\text{C}$  COSY spectrum of this diastereoisomer were of poor quality and a full assignment was not possible. The  $^1\text{H}$  spectrum and the  $^1\text{H}$ - $^1\text{H}$  COSY spectra were too complex to be interpreted in the absence of the  $^1\text{H}$ - $^{13}\text{C}$  COSY spectrum.





Scheme 4.8 Comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts of the later-eluted diastereoisomer of **10c** with those of menthol

The SiCH<sub>3</sub> signals of the two diastereoisomeric derivatives of racemic **10** were distinct and, as would be expected, had  $\delta_{\text{H}} \approx 0$  ppm. In the spectrum of native menthol, one of the *isopropyl* CH<sub>3</sub> signals overlapped with that from the lone methyl group. However, the diastereoisomers of **10c** produced quite dissimilar patterns of CH<sub>3</sub> signals. While the signal from the lone methyl group was unaffected by derivatisation, the *isopropyl* methyl groups were all shielded to different extents by the phenyl groups of the reagent. The later-eluted diastereoisomer had a CH signal at unusually high field (0.28 ppm), clearly an indication of shielding from the phenyl groups.

Similar conformationally dependent shielding effects have been noted previously, including those in derivatives of Mosher's acid,<sup>41</sup> which was discussed in the introduction. The Mosher's acid derivative of menthol compounds has been reported<sup>41, 183</sup> where some chemical shift differences between diastereoisomeric derivatives were as great as 0.32

ppm. Another menthol derivative, that of an axially chiral binaphthyl carboxylic acid, induced shielding to the extent that the methylene proton immediately between the C-O and the C-lone methyl of the menthyl derivative was observed at -0.23 ppm.<sup>45</sup>

#### *Effect of Temperature on the <sup>1</sup>H NMR Spectrum of 10c*

The large differences between the shifts of the two diastereoisomers on **10c** could have been due a difference in preferred conformation. The NMR spectrum was recorded at 20°C, 30°C and 40°C. No significant differences were observed in the spectrum. This suggests that, unless the barriers to conformational change were extremely large, the chemical shift differences between the two diastereoisomers on **10c** were not due to conformational differences.

#### *Summary of the GC and HPLC separations of 10a-c*

A summary of the GC and HPLC separations of **10a-c** is given in Table 4.17. For comparison, data are included from **10j**, the product of 3-pentanol and **10**.

As has already been discussed for most derivatives of **10**, the products of the *meso*-isomers of **10** were extremely well resolved from those of racemic **10**. This series of derivatisations was conducted over a wide time-span, with analyses at different conditions. The data selected for this table relate to experiments where the product mixtures were analysed under the same GC conditions.

Compound	GC $t_R$ / min GC method C:(60→250°C@10°C min <sup>-1</sup> )	HPLC $t_R$ / min (HPLC mobile phase)
<b>10a</b>	1377, <u>1425</u> , 1460	6.3, <u>7.1</u> , 7.8 (25%DCM/hexane)
<b>10b</b> (prepd from pure (rac)-10)	---, <u>1385</u> , --- (no <i>meso</i> -products)	---, <u>17.6</u> , <u>18.4</u> , --- (partial resolution - 1%DCM/hexane)
<b>10c</b> (earlier prep from mixed isomers of 10)	1455, <u>1516</u> , 1581	No HPLC data from this prep.
<b>10c</b> (prepd from pure (rac)-10)	---, <u>1500</u> , --- (no <i>meso</i> -products)	---, <u>15.4</u> , <u>17.0</u> , --- (baseline resolution - 5%DCM/hexane)
<b>10j</b> (3-pentanol deriv)	1136, <u>1159</u> , 1175	---, <u>6.2</u> , 8.8 (6%DCM/hex)

Table 4.17 GC and HPLC retention times of the resolved components of **10a-c**

*Retention times of the diastereoisomeric products believed to be derived from racemic 10 are underlined.*

*Circular dichroism spectroscopy of the diastereoisomeric derivatives of 10c:*

The resolved enantiomers of the parent silane **7** had equal and oppositely signed CD signals at 193, 203 and 231 nm. These were due to the two phenyl chromophores in their particular similar asymmetric environments. It was hoped that the CD at the higher wavelength would be fairly independent of substitution at silicon, because it would be further removed from the higher energy transitions associated with ethers. This would provide a means of comparing the absolute stereochemistry of the resolved diastereoisomeric derivatives with the resolved enantiomers of **7**. The CD and UV data for the stereoisomers of **10c** and **7** are shown in Table 4.18.

The two diastereoisomers of **10c** had approximately equal and opposite molar CD signals at 232 nm (Table 4.18). These were at the same  $\lambda_{\max}$  as for **7** and were of the same order of

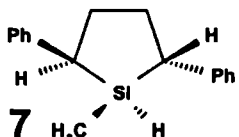
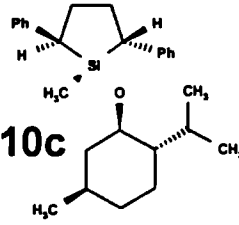
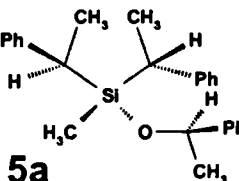
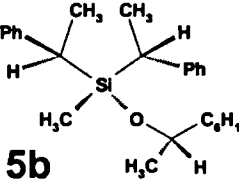
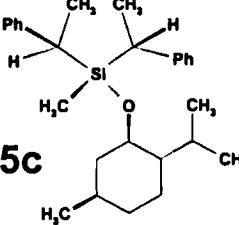
magnitude, which strongly supports the proposed correlation. However, there was a small difference. The molar CD values of the diastereoisomers of **10c** were only *ca.* 60% of that of the enantiomers of **7**, which was unexpected. This apparent minor discrepancy was accompanied by a 40% reduction in the molar absorptivity. The reduction in CD was probably a direct consequence of the reduction in absorptivity. Calculating the anisotropy factor,  $g = \Delta\epsilon/\epsilon$ , gives values for the diastereoisomers of **10c** which were within 70% of those for the enantiomers of **7**, which was considered to be close enough to relate the stereochemistry of the compounds **7** and **10a-c**.

*Summary of circular dichroism data from resolved enantiomers and diastereoisomers*

All the CD data associated with this work is summarised in Table 4.18. As discussed above, it is possible to relate the absolute configuration of the resolved enantiomers of the cyclic silane, **7** with the resolved diastereoisomers of its menthyl ether derivative **10c**, on the basis of  $\Delta\epsilon_{232}$  or  $g (= \Delta\epsilon/\epsilon)$ . However, it was not possible to make the same comparison with the diastereoisomeric fractions of **5a-c**.

**5a** had only been prepared from the racemic alcohol and racemic **5**, so no CD was expected, as each diastereoisomer would be formed to the same extent as its enantiomer. In the case of the fractions from **5b**, the ratio of  $\Delta\epsilon$  to  $\epsilon$  was approximately one order of magnitude different from that ratio of the resolved enantiomers of **7** ( $\Delta\epsilon/\epsilon=3.7\times10^{-4}$ ) or its menthyl ether **10c** ( $\Delta\epsilon/\epsilon=4.7\times10^{-4}$ ). It seems reasonable to suggest that the CD of acyclic **5b** isomers was related to that of **7** and **10c**, but was reduced in intensity by the lack of conformational rigidity in the acyclic system. The freedom for rotation about the Si-C bond may, in itself, have reduced the molar CD, or the presence of substituents at Si may have created a preference for a conformation that could only be achieved by the acyclic compound. From the NMR spectra, the first fraction of **5c** was believed to be derived from

one of the *meso*-isomers of **5** and the second from racemic **5**. As discussed in Section 4.1.11, both fractions had a negative CD, whereas the second fraction might have been expected to have a CD approximately zero. This showed that the menthyl group had a strong influence on the molecular conformation.

Compound	Stereoisomer	$\Delta\epsilon_{232\text{nm}}$	$\epsilon_{232\text{nm}}$	$g = \Delta\epsilon/\epsilon$
 <b>7</b>	Fraction #1	+7.5	20 400	$+3.7 \times 10^{-4}$
	Fraction #2	-6.9	20 800	$-3.3 \times 10^{-4}$
 <b>10c</b>	Fraction #1	-4.0	7 700	$-5.2 \times 10^{-4}$
	Fraction #2	+4.1	8 600	$+4.7 \times 10^{-4}$
 <b>5a</b>	HPLC fraction #1	0	14 800	0
	HPLC fraction #2	racemic !	14 300	racemic !
 <b>5b</b>	HPLC fraction #1	-1.1	15 800	$-7.2 \times 10^{-5}$
	HPLC fraction #2	+0.5	14 800	$+3.6 \times 10^{-5}$
	HPLC fraction #3	nd	nd	$+3.2 \times 10^{-5}$
 <b>5c</b>	HPLC fraction #1	nd	nd	$-7.5 \times 10^{-5}$
	HPLC fraction #2	-1.5	15 000	$-1.0 \times 10^{-4}$

nd:  $\Delta\epsilon$  or  $\epsilon$  not determined because insufficient sample available for accurate weighing.

#1, #2 and #3 are first, second and third eluted fractions

Units of  $\Delta\epsilon$  and  $\epsilon$  are  $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$

Table 4.18 UV and CD data for some of the resolved enantiomers and diastereoisomers in this study.

## 4.2 FURTHER INVESTIGATIONS INTO GC SEPARATION OF DIASTEREOISOMERS

### 4.2.1 *Further investigation into the GC of 10c diastereoisomers*

Because of the difficulty in obtaining any resolution of **10c** diastereoisomers by GC, the possibility that they interconverted or that they both converted to a common rearrangement product was considered. The EIMS of the eluted product gave an abundant molecular ion and fragmentation pattern that was acceptable for **10c**. That the spectrum was identical when either diastereoisomer was injected was not unexpected. It was possible that rapid rearrangement in the injector to a common product had occurred. On the other hand, decomposition of two resolved diastereoisomers near the end of the column, or in the transfer line (to the mass spectrometer), or in the mass spectrometer itself would still be expected to produce two peaks. On-column interconversion of two well-separated compounds would normally lead to two GC peaks, linked by a plateau. The plateau region arises from molecules that have existed as both compounds during the timeframe of the analysis. To investigate the possibility that any of these possible rearrangements may have taken place somewhere in the GC/MS, a system was devised that would mimic the GC conditions, with the scope to examine the products. A Perkin-Elmer 8410 GC instrument was set up to perform small-scale preparative GC, at a scale large enough to collect products for NMR analysis. An AQ1 (BP1-equivalent) capillary, 12m × 0.53 mm (1.0 µm film thickness) was fitted to an injector at 250°C operated in splitless mode, with helium carrier gas and an FID detector at 275°C. Initial tests confirmed that there was reasonable chromatographic behaviour and allowed the loading to be studied. Samples of the resolved diastereoisomers of **10c** from the HPLC purification were dissolved in hexane. In turn, they were injected onto the column, which was temperature programmed from 100°C (held for 10 min), -> 260°C @ 30°C min<sup>-1</sup>. The fractions produced peaks at 20.2 min, with a narrow

peak (width = *ca.* 0.8 min) at loadings  $\leq 50$   $\mu\text{g}$ . The loading was increased to 0.5 mg, whereupon the peak width increased to 2.7 min. Because the fractions were very pure, there was no need to specially select the region of the temperature program at which to trap the product fraction. The column was separated from the detector and connected to a 1 m length of 0.53 mm internal diameter deactivated silica tubing, arranged so that most of it was outside the column oven. Shortly after injection of the diastereoisomer, the odour of the solvent vapour was apparent at the trap exit. The trap was then chilled in solid  $\text{CO}_2$  until 5 minutes after the diastereoisomer was expected. The chilling proved unnecessary, as the product could be clearly seen as a small drop in that part of the capillary that was between the column oven and the solid  $\text{CO}_2$ . After washing the trapped product from the capillary with  $\text{CDCl}_3$ ,  $^1\text{H}$  NMR analysis (Figure 4.17) showed conclusively that each diastereoisomer emerged from the column unchanged (compare with Figure 4.16).

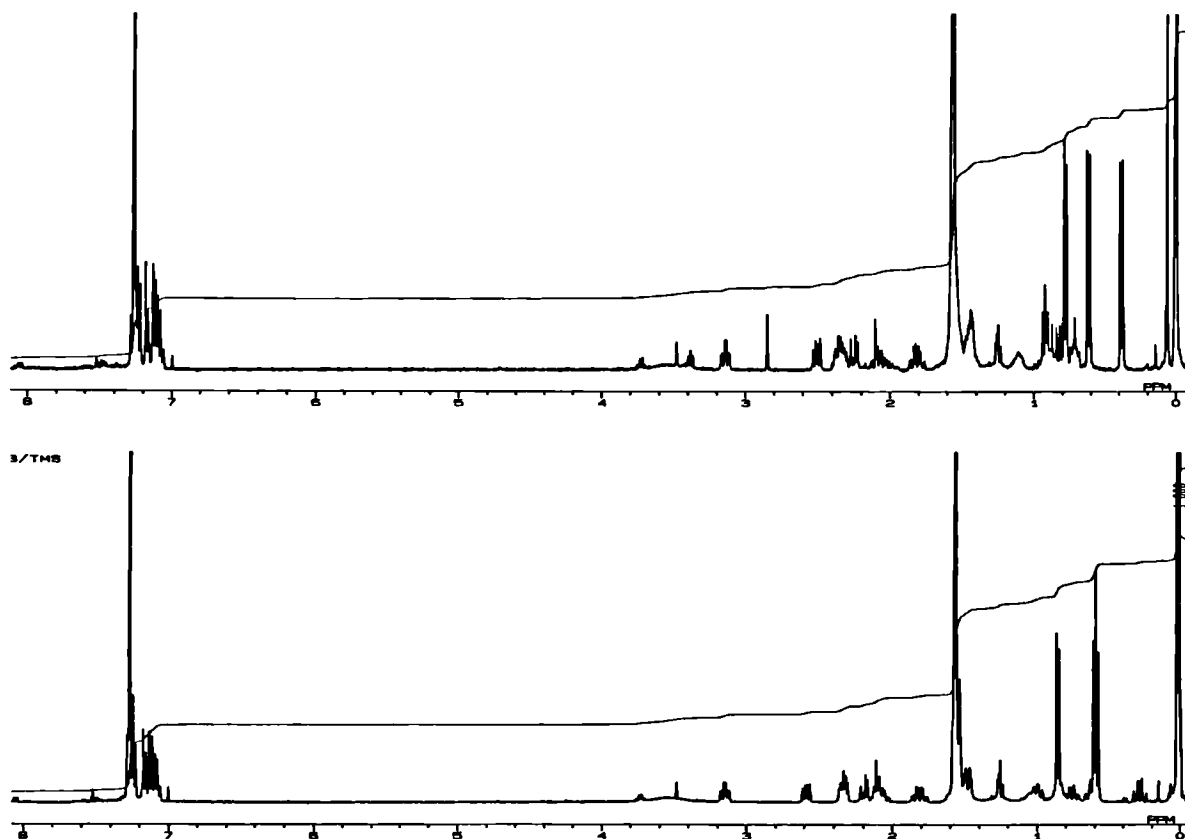


Figure 4.17 The  $^1\text{H}$  NMR spectra of the diastereoisomers of **10c** following elution by gas chromatography. (The signal at 1.6 ppm is due to water).

This experiment strongly suggested that there was no on-column rearrangement. Although the experimental conditions closely resembled normal GC there were still differences, particularly the silyl ether concentration. In the preparative GC, the stationary phase would be totally coated with the silyl ether, so that the majority of silyl ether molecules would not experience any interactions on the stationary phase. The resolved diastereoisomers were re-analysed by GC/MS and gave identical GC and EIMS profiles, which was not unexpected. NMR spectra of the two fractions provided conclusive evidence that they were indeed the resolved diastereoisomers of **10c**.

#### 4.2.2 *Further Attempts To Resolve Diastereoisomeric Products By GC*

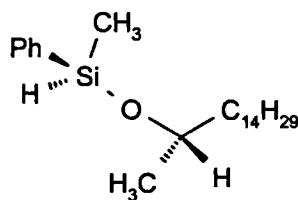
The diastereoisomers of compounds **3a-c**, **5a-c**, and **10a-c** were unresolved under the standard conditions used for reaction monitoring and product identification by GC/MS. However, these conditions were designed to provide a general method for separation of a wide range of compounds and were not optimised for separation of the diastereoisomers. Further attempts at separation of the diastereoisomers are summarised in Table 4.20.

Compound	GC column	GC conditions	$t_R$ / s	Comments
<b>5a</b>	BPX70 12m × 0.32mm	60°C for 1 min; →190°C at 30°/min; 190°C →250°C at 2°/min	673	diasts unresolved
<b>5a</b>	BPX5 25m × 0.25mm	60°C for 1 min; →240°C at 30°/min; 240°C →250°C at 2°/min	915	diasts unresolved
<b>10a</b>	DB1701 25m × 0.25mm	150°C →250°C at 5°/min	1664	diasts unresolved
<b>10b</b>	BP5 25m × 0.33mm	200→230°C at 1°C / min	1229	diasts unresolved
<b>10b</b>	CP Sil8 CB 50m × 0.22mm	150°C →275°C at 5°/min Carrier gas H <sub>2</sub>	1356	diasts unresolved
<b>10b</b>	BP10 25m × 0.22mm	150°C →250°C at 5°/min Carrier gas H <sub>2</sub>	1586	diasts unresolved



Compound	GC column	GC conditions	$t_R$ / s	Comments
10c	BP5 25m × 0.33mm	60°C → 250°C at 10°/min	1552	diasts unresolved
10c	BP5 25m × 0.33mm	150°C → 230°C at 5°/min	2329	diasts unresolved
10c	BP5 25m × 0.33mm	230°C → 250°C at 1°/min	774	diasts unresolved
10c	BP5 25m × 0.33mm	60°C → 230°C at 40°/min; 230°C → 250°C at 1°/min	1017	diasts unresolved
10c	DB5 60m × 0.25mm	260°C for 5 min; 260°C → 285°C at 1°/min	1534	diasts unresolved
10c	BPX5 25m × 0.25mm	60°C for 3 min; → 250°C at 40°/min	1114	diasts unresolved
10c	BPX5 25m × 0.25mm	60°C for 3 min; → 250°C at 40°/min	995	diasts unresolved
10c	CP Sil8 CB 50m × 0.22mm	200°C → 275°C at 5°/min Carrier gas H <sub>2</sub>	928	diasts unresolved
10c	BP10 25m × 0.22mm	150°C → 250°C at 5°/min Carrier gas H <sub>2</sub>	1075	diasts unresolved
10c	BPX70 12m × 0.32mm	85°C for 1 min; → 180°C at 20°/min; 180°C → 250°C at 1°/min	914	diasts unresolved
10c	DB1701 25m × 0.25mm	150°C → 250°C at 5°/min	1727	diasts unresolved

Table 4.20      Alternative conditions for attempted GC separations of diastereoisomeric silyl ethers.



It was impossible to resolve most of the diastereoisomeric silyl ethers by GC, apart from those containing the  $\text{PhSiHCH}_3\text{O-}$  group (compounds **1a-c**). One potential reason was that these ethers (compounds **3a-c**, **5a-c**, and **10a-c**) were of lower volatility, and, at the higher temperature required to elute them, the diastereoisomers may have behaved in a more similar manner on the chromatographic stationary phase, as they adopted a more similar average conformation.

An alternative explanation is that the higher elution temperatures required for larger homologues would be expected to reduce the selectivity because, as analyte-stationary phase interactions become weaker, so the interaction of one diastereoisomer with the stationary phase would become more similar to that of the other. A similar result, attributed to the effect of temperature, was shown by Schurig<sup>184</sup> to occur on the chiral GC phase, Chirasil-Nickel, where the selectivity was dramatically increased between the GC separation at 150°C and the SFC separation at 40°C.

A long chain alcohol, 2-hexadecanol, was selected to prepare a higher-boiling derivative of the chloromethylphenylsilane, in an attempt to test this hypothesis.

$^1\text{H}$  NMR of the reaction products of 2-hexadecanol and chloromethylphenylsilane (**1**) showed that the two diastereoisomers of methylphenylsilyl 2-hexadecyl ether (**1k**) were formed, and were present in equal proportions. As was found for the homologous diastereoisomeric ether formed from this chlorosilane (*i.e.* **1b**), the two  $\text{SiCH}_3$  groups were isochronous (in both the  $^1\text{H}$  and the  $^{13}\text{C}$  spectra) while the diastereoisomeric  $\text{C}_1$ -methyl proton signals were distinct ( $\Delta\delta_{\text{H}} = 0.04$  ppm). Considering the two diastereoisomers, the isochronicity of the  $\text{SiCH}_3$  groups and the anisochronicity of the  $\text{C}_1\text{CH}_3$  groups was

assumed to be due to the diamagnetic effect of the phenyl group, which would be more different between the CCH<sub>3</sub> groups of the two diastereoisomers than it would between the SiCH<sub>3</sub> groups.

As was the case for **1b**, GC easily resolved the two diastereoisomers. The larger  $\Delta t_R$  for **1k** (10 s compared with 3 s) was presumably due to the fact that both compounds were run under the same GC conditions, with **1b** being eluted very soon after the steep thermal gradient, clearly sub-optimal for this less volatile homologue. ( $t_R \approx 500$  s, compared with the  $t_{maxT}$  at 465 s). The GC retention times of silyl ethers run under the same conditions are compared in Table 4.20.

	<b>a</b>	<b>b</b>	<b>c</b>	<b>k</b>
<b>1</b>	516, 519	499, 502	534	773, 783
<b>3</b>	560	542	589	NP <sup>1</sup>
<b>5</b>	919	849	991	NP <sup>1</sup>
<b>10</b>	NR <sup>2</sup>	(620) <sup>3</sup>	1209	NP <sup>1</sup>

Table 4.20 Comparison of GC retention times of silyl ethers run under same conditions  
GC method B: 60 °C for 3 min, →250 °C at 40 °C min<sup>-1</sup>

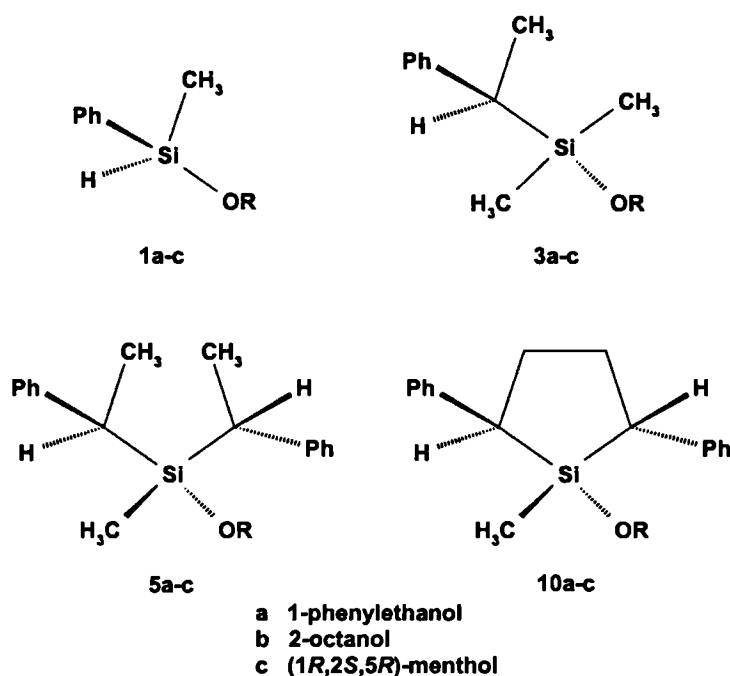
- Notes: 1. Not prepared  
2. GC not recorded under similar conditions  
3. Slight change to GC method (no hold at initial temperature). With 3 minute delay, equivalent  $t_R \approx 800$  s.

The fact that the less volatile diastereoisomeric derivatives, **1k**, were well resolved suggested that the lack of resolution of the diastereoisomeric derivatives **3a-c**, **5a-c** and **10a-c** was not simply the result of increased conformational similarity of the diastereoisomers or reduced analyte-stationary phase interactions at higher temperatures. It appeared that there were fundamental differences between the adsorption of the ethers

derived from **1** and those derived from **3**, **5** and **10**. This observation is not surprising, because **1** is the only chlorosilane with the chiral centre adjacent to the ether bond; the others all have a more remote chiral centre.

#### 4.3 SUMMARY OF THE ANALYTICAL RESULTS FROM THE DIASTEREOISOMERIC DERIVATIVES PREPARED FROM CHIRAL CHLOROSILANES

The alkoxysilanes generated were numbered on the basis of their parent chlorosilanes **1**, **3**, **5** and **10** and the alcohols, as shown in Scheme 4.9. In the chemical structures shown here, one stereochemical form may be shown, but in general this should be taken to represent a mixture of all the possible stereoisomers, unless specifically noted to the contrary.



Scheme 4.9 Diastereoisomeric alkoxysilanes investigated in this work

Adequate evidence, particularly from NMR and EIMS, was obtained for the preparation of the diastereoisomeric alkoxysilanes shown in Scheme 4.9. The ability to distinguish the diastereoisomers arising from the enantiomers of each alcohol was of paramount interest in this research. The results from the NMR spectroscopic, HPLC and GC analysis is summarised in Table 4.21.

	NMR	GC	HPLC
<b>1a</b>	Diastereoisomers differentiated	Diastereoisomers resolved $\alpha = 1.006$ $R_s = 1.30$	Not successful: poor hydrolytic stability of Ph-Si-O- derivatives
<b>1b</b>	Diastereoisomers differentiated	Diastereoisomers resolved $\alpha = 1.006$ $R_s = 1.41$	
<b>1c</b>	Diastereoisomers differentiated	Diastereoisomers not resolved	
<b>3a</b>	Diastereoisomers differentiated	Diastereoisomers not resolved	Partial resolution of diastereoisomers $\alpha = 1.07$ $R_s \approx 0.7$
<b>3b</b>	Diastereoisomers differentiated	Diastereoisomers not resolved	Partial resolution of diastereoisomers $\alpha = 1.06$ $R_s$ not quantifiable
<b>3c</b>	Diastereoisomers differentiated	Diastereoisomers not resolved	Diastereoisomers not resolved
<b>5a</b>	Diastereoisomers differentiated	Diastereoisomers arising from chiral chlorosilane <b>4</b> probably not resolved. Derivatives of geometric isomers of <b>4</b> were resolved.	Diastereoisomers arising from chiral chlorosilane <b>4</b> probably not resolved. Derivatives of geometric isomers of <b>4</b> were resolved.
<b>5b</b>	Diastereoisomers differentiated		
<b>5c</b>	Diastereoisomers differentiated		
<b>10a</b>	Diastereoisomers differentiated	Diastereoisomers arising from chiral chlorosilane <b>10</b> not resolved. Derivatives of geometric isomers of <b>10</b> were resolved.	Diastereoisomers arising from chiral chlorosilane <b>10</b> probably not resolved
<b>10b</b>	Diastereoisomers differentiated		Partial resolution of diastereoisomers of <b>10b</b> , $\alpha = 1.06$
<b>10c</b>	Diastereoisomers differentiated		Diastereoisomers of <b>10c</b> well resolved, $\alpha = 1.006$ $R_s = 1.41$

Table 4.21 Summary of the analytical results from the diastereoisomeric derivatives prepared from chiral chlorosilanes

The implications for potential analytical applications are discussed in chapter six.

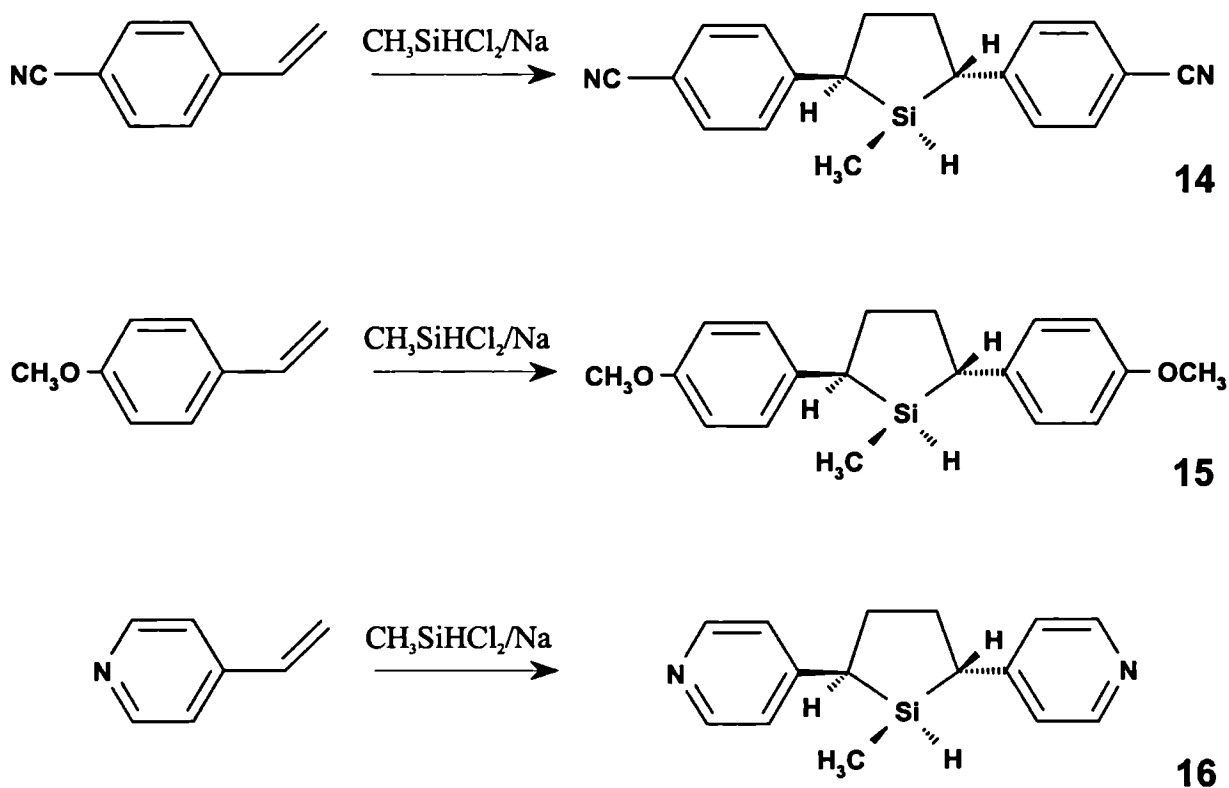
## CHAPTER 5

### ATTEMPTED PREPARATION OF OTHER CYCLIC CHLOROSILANES

#### 5.1 Introduction

The compound originally expected to be the most promising of the chlorosilane reagents described so far (10) failed on two counts. Most importantly, diastereoisomeric derivatives prepared from a small selection representing typical chiral alcohols failed to be resolved by GC. Secondly, the yield of the silane precursor was low.

Compounds related to styrene (Scheme 5.1) were used in an attempt to remedy these problems. The three compounds described were expected to behave differently with respect to both the coupling / cyclization reaction and to the differentiation of diastereoisomers by GC for electronic, rather than steric reasons.



Scheme 5.1 Preparation of modified cyclic chlorosilanes

In the first example, 1-methyl-2,5-di-(4-cyanophenyl)silacyclopentane (**14**), the nitrile group was expected to stabilise the dimeric radical carbanion intermediate, thus hopefully reducing the tendency to polymerisation.

Although this benefit was not expected in the case of 1-methyl-2,5-di-(4-methoxyphenyl)silacyclopentane (**15**), this compound was considered in the hope that the diastereoisomeric derivatives that would be prepared from the chlorosilane would be better distinguished by GC. In this regard, the 2-substituted analogues of the precursor styrene would be expected to be more successful, providing more steric crowding in both cases, but the 4-substituted compounds were used because they were commercially available.

### 5.2 *Attempted preparation of 1-methyl-2,5-di-(4-cyanophenyl) silacyclopentane (14)*

The preparation of **14** was attempted using the same procedure as was used in the synthesis of **6**. Despite the poor yield in the preparation of **6**, the product was readily observed by GC/MS and by NMR. However, the reaction of 4-cyanostyrene with sodium and dichloromethylsilane did not give any similar characteristic evidence for the formation of **14**. There were no sharp signals in the region upfield of 0.6 ppm in the spectrum that might have corresponded to the expected SiHCH<sub>3</sub> doublet. There was also no sign of any peaks in the GC/MS that corresponded to the anticipated molecular ion, despite running the GC up to a higher temperature (270°C) than was adequate to elute **6**. Broad bands in the NMR suggested the formation of polymeric products.

### 5.3 *Attempted preparation of 1-methyl-2,5-di-(4-methoxyphenyl) silacyclopentane (15)*

With similar experimental conditions used for the preparation of **6**, and for the attempted preparation of **14**, the preparation of **15** was unsuccessful. This conclusion was based on the same criteria as in the previous section, *i.e.* that the desired silacyclopentane product would a) be expected to have a sharp NMR doublet at *ca.* 0 ppm corresponding to the

expected SiHCH<sub>3</sub> doublet, and b) have a peak in the GC/MS with a distinct EI molecular ion. Again, the production of a large amount of precipitate during the reaction appeared to be due to the formation of polymeric by-products. The reaction was attempted using either sodium or potassium, but to no avail.

#### 5.4 *Attempted preparation of 1-methyl-2,5-di-(4-pyridyl)silacyclopentane (16)*

##### *From 4-vinylpyridine and dichloromethylsilane*

Initial experiments to produce **16** were based on the preparation of the cyclic silacyclopentane, **6**. However, mixtures of 4-vinylpyridine and dichloromethylsilane added to sodium in THF resulted in none of the desired cyclic product. This was deduced on the assumption that the product would have two distinctive features: a) a strong molecular ion in the EIMS and b) a SiCH<sub>3</sub> doublet in the <sup>1</sup>H NMR spectrum at *ca.* 0 ppm. The experiment was repeated with specially dried 4-vinylpyridine in different ways: a) 4-vinylpyridine was added to a mixture of sodium spheres and dichloromethylsilane in THF; b) dichloromethylsilane was added dropwise to a sodium dispersion in THF containing 4-vinylpyridine at -30 to -60°C; c) 4-vinylpyridine was added slowly to a sodium dispersion in THF at 20°C. After stirring overnight, the dichloromethylsilane was added; d) 4-vinylpyridine and dichloromethylsilane were added together to stirred sodium spheres in THF.

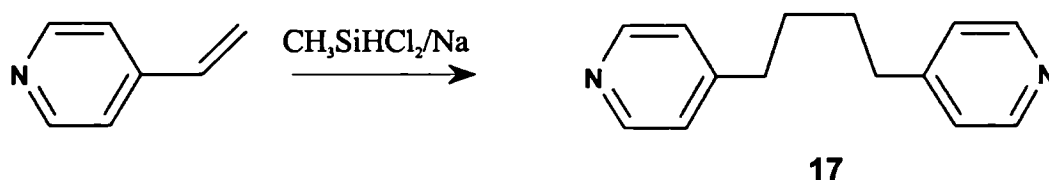
Sodium dispersions were prepared as described by Frank *et al.*,<sup>185</sup> such that the mean diameter was < 1mm in order to maximise the metal surface area. Sodium spheres were heated in oil above their melting point with vigorous stirring to produce an emulsion. The stirrer was stopped and the mixture allowed to cool in air. To minimise contact with air, this procedure was carried out in the flask to be used for the reaction, the oil being



displaced from the sodium dispersion by successive washes with dry THF *via* PTFE tubes sealed into the system.

Samples of reaction mixture were prepared for analysis by suspending in CDCl<sub>3</sub>, washing with D<sub>2</sub>O before analysing by NMR and GC/MS.

The major product, which was purified but not isolated at this stage, appeared to be the 1,4-disubstituted compound, *i.e.* 4,4'-(1,4-butanediyl)bipyridine (**17**), evidence that the reaction was successful in the first stage only, as outlined in Scheme 5.2. Instead of reacting with the chlorosilane, the organosodium intermediate abstracted a proton from the reaction medium, or from adventitious water.



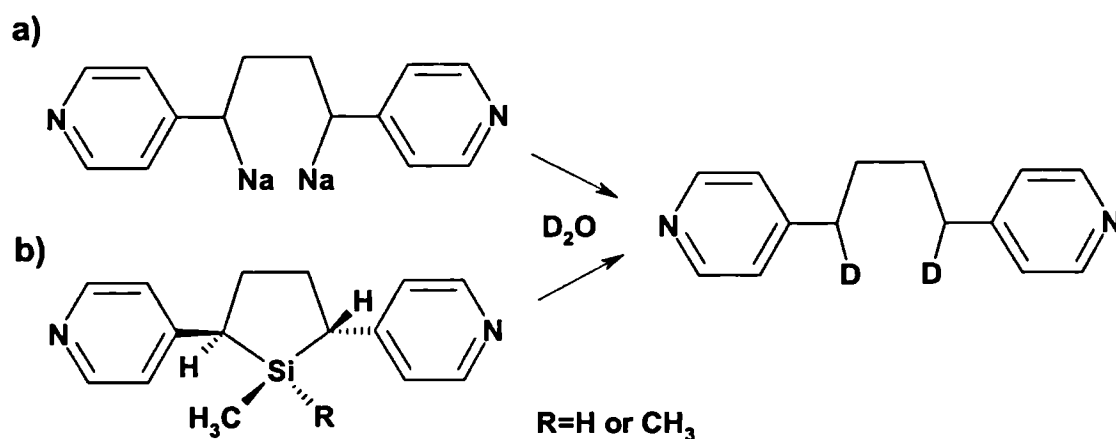
Scheme 5.2 Product formed in the attempted cyclisation of 4-vinylpyridine with dichloromethylsilane.

Subsequent search of the literature revealed that this compound had been prepared by similar means (albeit without the chlorosilane!). This is discussed later in this chapter.

An analogue was also detected in the EIMS, being 4,4'-(1,3-propanediyl)-bis-pyridine. This was more apparent in some of the older extracts from alkaline solutions of products of the reactions from sodium dispersions (although this may have been coincidental). Rather than being an initially-formed product (which would require the loss of a methyl group), this was perhaps the result of decomposition of a larger by-product. This would be interesting if it represented a silicon-containing polymeric by-product, because it suggests head to tail polymerisation, which may be the favoured route which competes with the desired head to head polymerisation.

The relative ease of preparation of the dimethylsilane vs. the methylsilane compounds **6** and **12** has already been noted. On the basis that similar factors would affect the outcome of the present reactions, an analogous reaction was carried out to prepare the 1,1-dimethyl-2,5-di-(4-pyridyl)silacyclopentane. This too was unsuccessful, although the product may have been formed briefly, then decomposed, using the procedures discussed above. The increase in viscosity of the reaction mixture after 90 minutes was probably a good indication of the formation of polymeric by-products.

Another interesting feature that arose in this work resulted from the use of D<sub>2</sub>O (for the sake of the NMR) in the acid/base extractions of product mixtures. Depending on the circumstances of the work-up of a particular fraction, some were found to consistently contain molecular ions for the 4,4'-(1,4-butanediyl)bipyridine component with an m/z value one or two units higher than expected. There was a mixture of bisdeuterated, monodeuterated and nondeuterated product. The fragments present in 4,4'-(1,4-butanediyl)bipyridine were observed here, accompanied by their monodeuterated analogues. This was interpreted as being due to the diorganosodium intermediate having reacted with D<sub>2</sub>O as outlined in Scheme 5.3a.



Scheme 5.3 Origin of higher-mass by-products following D<sub>2</sub>O extractions

It was also possible that the bisdeuterium compound could have arisen from the solvolysis of the cyclic product, as shown in Scheme 5.3b, although the cyclic compound was only

observed in one GC/MS of the very large number of such analyses from many related reactions. Another possible source was any silyl/pyridyl polymer that may have been present. In any case, the route in Scheme 5.3a was shown to operate in later experiments.

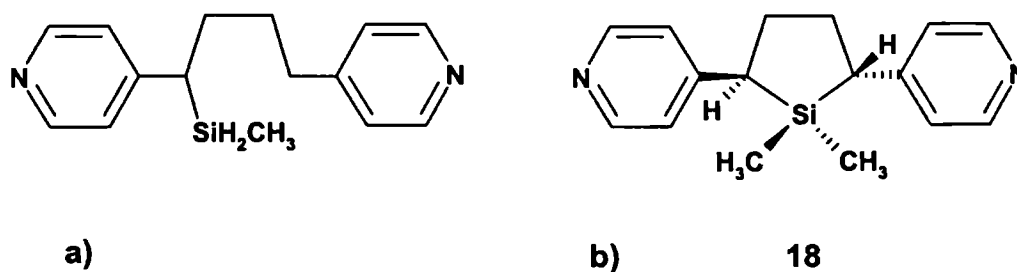
The deuterium atoms were shown to be incorporated at carbon (rather than nitrogen). The compound was extracted from aqueous solution (basified with ammonia) into  $\text{CH}_2\text{Cl}_2$ , then extracted back into aqueous acid (HCl). The molecular ion still occurred at  $m/z$  214, proving that the deuterium was not exchangeable.

In subsequent work, 4,4'-(1,4-butanediyl)bipyridine (**17**) was deliberately prepared and, *via* the diorganometallic intermediate, the bisdeuterated compound was isolated. This allowed further confirmation of the structure by  $^1\text{H}$  and  $^{13}\text{C}$  NMR. In particular, the distinct coupling of carbon to deuterium (routine H-decoupled, D-nondecoupled) in the  $^{13}\text{C}$  spectrum confirmed the position of deuteration as being that shown in Scheme 5.3.

The GC/MS also supported this analysis, the deuterated product from dilithiated **17** having an EIMS molecular ion two amu higher and fragments one amu higher than for the native **17**, (*e.g.* an ion at  $m/z$  40, being due to  $[\text{C}_3\text{H}_2\text{D}]^+$ , with a high relative abundance, similar to that of  $[\text{C}_3\text{H}_3]^+$  in **17**).

In the course of this work, brief observations were made by GC/MS of some of the target compounds (containing the 4-pyridyl-CH-Si group). Their rare and normally unrepeatably appearance could have been a result of the easy acidic cleavage of the C-Si bond in these compounds (protonation at nitrogen allows rapid attack by solvent in these systems<sup>186</sup>).

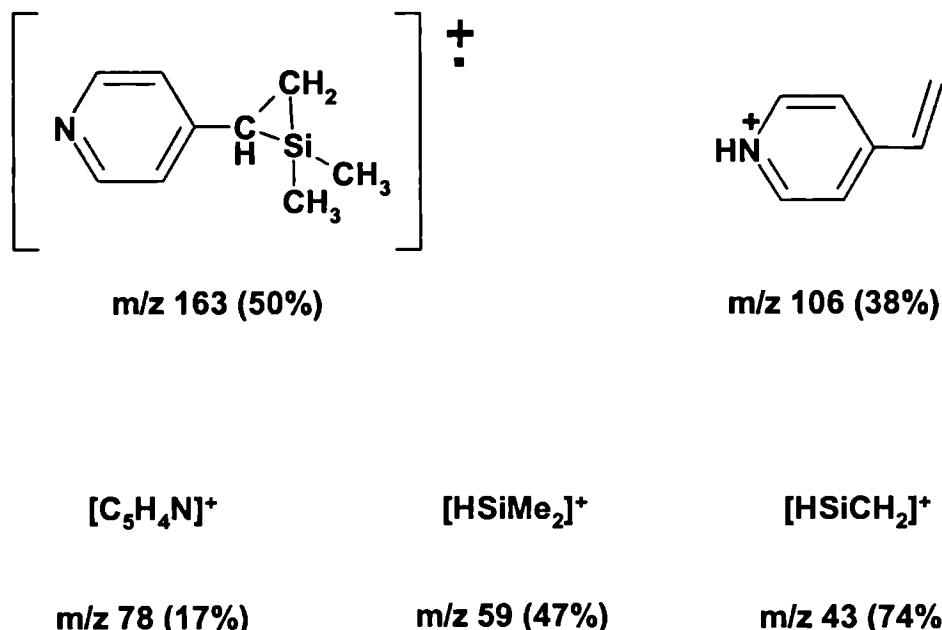
Compounds of this type believed to have been formed are shown in Scheme 5.4.



Scheme 5.4 Tentative structures of products containing the pyridyl-CH-Si group formed during the reaction of 4-vinylpyridine with a) methylsilane and b) dimethylsilane.

Evidence for these compounds came from the EIMS data. The compound shown in Scheme 5.4a had a molecular ion with  $m/z$  256 and major fragments at  $m/z$  150 (base peak) and 106 (75%). The base peak could have been formed by loss of the pyridyl analogue of a styrene radical,  $[C_5H_4N.CH_2CH_2]^\cdot$ , (there was the same loss in the fragmentation of 4,4'-(1,4-butanediyl)bispyridine (17)). The ion at  $m/z$  106 was probably the same as was seen from both 17 and 4,4'-(1,3-propanediyl)-bis-pyridine, being the cationic equivalent of the above radical, stabilised by rearrangement to be protonated at nitrogen,  $[C_5H_4NH.CHCH_2]^+$ .

The compound in Scheme 5.4b, 18, was also only seen once at this stage of the work, but the EIMS corresponded well with this structure. The molecular ion ( $m/z$  268) was the base peak; the assignment of fragments is shown in Scheme 5.5.

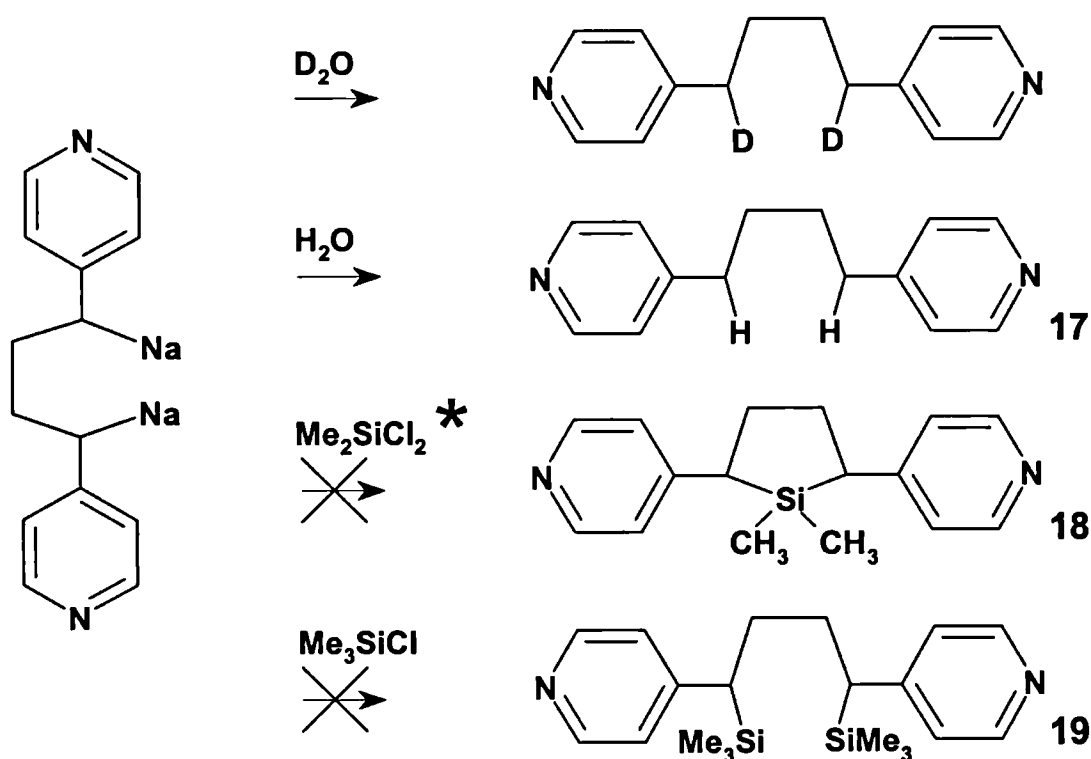


Scheme 5.5 Assignment of fragments of putative cyclic bispyridyl derivative.

The largest difference between the EIMS of this compound and that of the diphenyl equivalent (**12**) was that the latter had a base peak with  $m/z$  117,<sup>167</sup> assigned as  $[PhCHCHCH_2]^+$ . The pyridyl equivalent of this fragment was not present to any great extent in the putative cyclic bispyridyl compound. One possible reason for this was originally thought to be that this bispyridyl compound was the 2,4-disubstituted isomer (the base peak of 1,1-dimethyl-2,4-diphenylsilacyclopentane is at  $m/z$  162),<sup>172</sup> which would be equivalent to the fragment with  $m/z$  163 shown in Scheme 5.5. However, a subsequent preparation of a compound having a very similar EIMS and believed to be **18**, starting from 4,4'-(1,4-butanediyl)bispyridine (**17**), could only be expected to be the 2,5-disubstituted product.

Using similar approaches, attempts to repeat the preparation of **18** failed. The diorganosodium compound was shown to be present in reaction mixtures by addition of aliquots to  $D_2O$  and  $H_2O$ . The formation of  $PyCHD(CH_2)_2CHDPy$  and  $Py(CH_2)_4Py$  respectively proved a useful diagnosis and, under the reaction conditions typically used, confirmed that the reagent was still active after >2 days. However, when the same reagent

was added to either  $(\text{CH}_3)_2\text{SiCl}_2$  or  $(\text{CH}_3)_3\text{SiCl}$ , and the same extraction procedure used (mixed with ethyl acetate and separated by centrifuge) the expected products were not seen by GC/MS. There was no molecular ion or recognisable fragments (no  $[\text{M}-15]^+$ , for instance). In the case of the bis(trimethylsilyl) product there was no evidence for the mono-substituted TMS product either. These findings are summarised in Scheme 5.6.



Scheme 5.6 Reactions of bispyridyl diorganosodium compound

\* This product (**18**) only detected briefly at this stage of the work

In hindsight, these compounds may have been more frequently observed if the aqueous acid/base extraction work up had not been routinely used. Nevertheless, the small-scale experiments outlined in Scheme 5.6 used mild conditions and suggest some inherent difficulty with the preparation of these silicon compounds.

### 5.5 Preparation of 4,4'-(1,4-butanediyl)bipyridine (17)

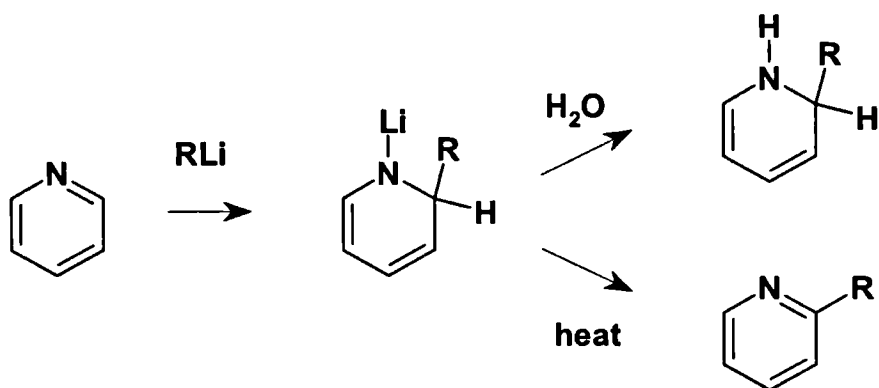
In the course of this work, it became apparent that the by-product, 4,4'-(1,4-butanediyl)bipyridine) (17), had already been prepared, and by a very similar route.<sup>187</sup> This preparation used the same starting material, 4-vinylpyridine, with lithium to generate the diorganolithium intermediate. 2-Methyl-2-propanol was included in the reaction mixture, to protonate the dicarbanion as it was formed. This procedure worked well, and allowed 17 to be isolated before the next stage.

### 5.6 Preparation of dilithiated 4,4'-(1,4-butanediyl)bipyridine and attempted silylation

#### i) Via butyl lithium

Initial attempts to prepare the diorganolithium intermediate from 17 were made using butyllithium. An aliquot of the reaction mixture was added to D<sub>2</sub>O, as described above. This showed that the starting material had reacted, but that the four products seen in the GC did not include the anticipated bisdeuterated product that would have been derived from the diorganolithium intermediate prepared previously. From the EIMS molecular ion and fragmentation pattern, the first-eluted compound appeared to be a monobutylated product of 17, there being losses of CH<sub>2</sub> units not seen with the parent or related compounds, although the molecular ion was difficult to assign. There was also some evidence for incorporation of deuterium. The other three components were probably dibutylated products. After adding dichloromethylsilane and stirring overnight, the test was repeated. A similar pattern of four GC peaks with related EIMS was obtained. The first-eluted compound had the same *t<sub>R</sub>* and a similar EIMS compared with that observed prior to the dichloromethylsilane addition, but with no evidence of deuterium. Of the three dibutylated products, the first (minor) and third (major) appeared to be isomers with RMM = 328. The test prior to the dichloromethylsilane addition generated compounds with RMM

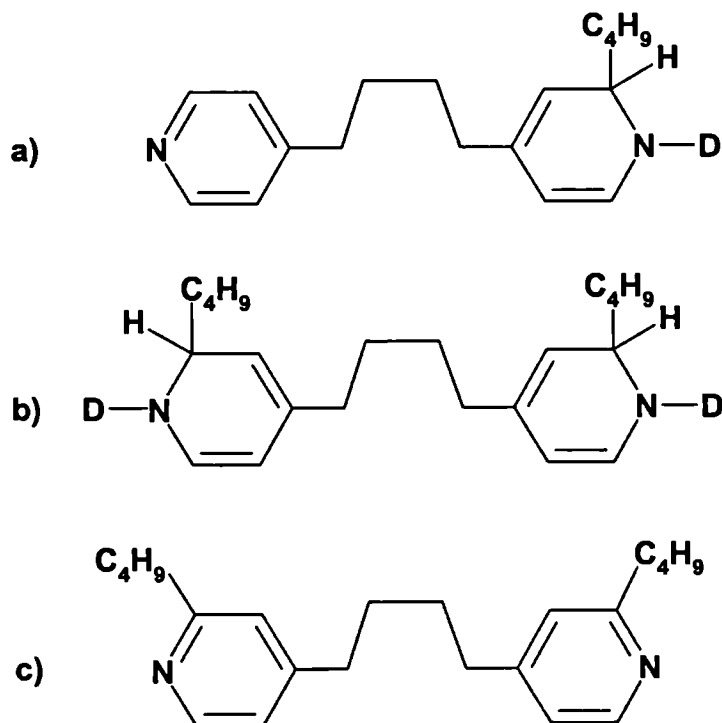
= 330. Only the second of the dibutylated products gave similar spectra before and after dichloromethylsilane addition. This absence of incorporation of deuterium proved that this product had not arisen from a reactive organolithium compound. Addition of alkyllithiums to aromatic compounds is not unprecedented<sup>188</sup> and proceeds as outlined in Scheme 5.7.



Scheme 5.7 Addition of alkyllithiums to pyridine

On the other hand, reactions under very similar conditions (hexane/THF mixtures) to those reported from this work have not been troubled by disubstitution of the pyridine ring.<sup>189</sup> On the basis of this and the EIMS data, the compounds were believed to have the structures in Scheme 5.8 (shown with deuterium uptake where this occurred). The monobutylated compound probably had the structure in Scheme 5.8a, although the EIMS evidence is not conclusive. The first of the dibutylated compounds was apparently an isomer of the third for which the EIMS corresponded well with the structure shown in Scheme 5.8b (base peak corresponding to  $[M-57]^+$ , and the second compound was probably as shown in Scheme 5.8c.





Scheme 5.8 Proposed structures for some of the alkylated by-products.

Although the EIMS evidence for all these structures was not conclusive, it was clear that an alternative approach was required to generate the desired diorganometal reagent.

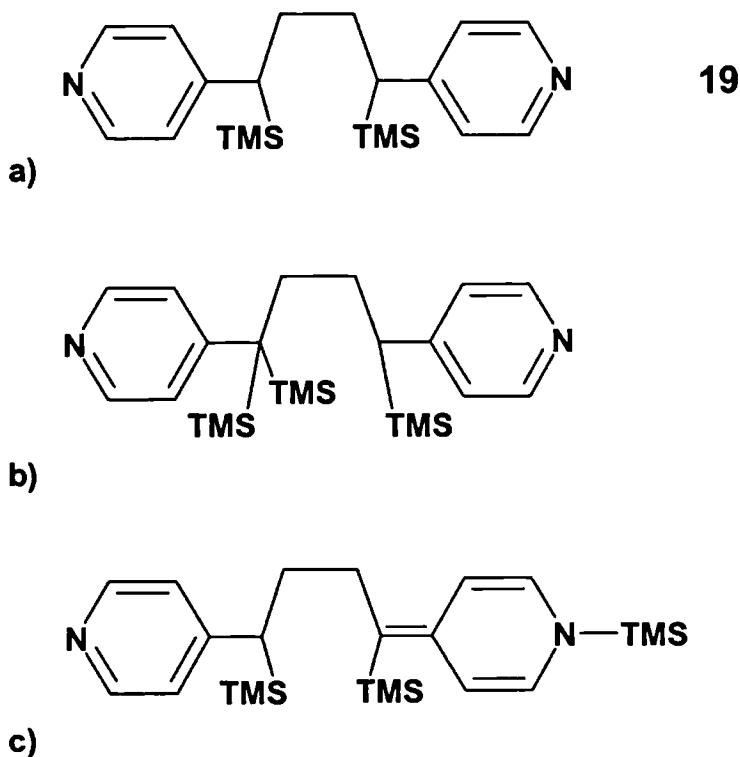
*ii) Via lithium di-iso-propylamide (LDA)*

The use of lithium di-*iso*-propylamide (LDA) as base was more successful. Initial attempts with old batches of LDA (solution in heptane/THF/ethylbenzene) produced some diorganolithium compound from 4,4'-(1,4-butanediyl)bispyridine ( $D_2O$  test), but mostly the monolithiated product. Of particular interest was the appearance of two isomeric impurities with an abundant molecular ion at  $m/z$  210 and base peak at  $m/z$  91 (tropyllium ion,  $[C_7H_7]^+$ ), and other phenyl-derived fragments. One of these was recognisable as 1,4-diphenylbutane (a by-product already reported from the reaction of styrene with alkali metal). This was unexpected and presumably arose from the ethylbenzene present in the commercial LDA solution. (In which case this would often occur as a by-product. This dimer could have been present in the reagent solution, or its production could have been

exacerbated by the particular conditions used here). The other isomer was believed to be 2,3-diphenylbutane. This also had an abundant molecular ion at  $m/z$  210, which fragmented to a tertiary ion ( $[\text{PhCHCH}_3]^+$ ) and radical ( $[\text{PhCHCH}_3]^\cdot$ ) to give the base peak at  $m/z$  105.

Continuing work with a fresh batch of LDA, the diorganolithium compound was conclusively produced from 4,4'-(1,4-butanediyl)bispypyridine (17) ( $\text{D}_2\text{O}$  test). Using dried glassware and syringes, it was possible to transfer this intermediate to conduct a number of small-scale tests on different chlorosilanes ( $(\text{CH}_3)_3\text{SiCl}$ ,  $(\text{CH}_3)_2\text{SiCl}_2$ ,  $\text{CH}_3\text{SiHCl}$ ). However, although a  $\text{D}_2\text{O}$  test at the end of the work validated the method, compounds containing both the silane moiety and the bispypyridyl- system were rarely seen by GC/MS. The test-scale reaction with chlorotrimethylsilane produced two later-eluting peaks in the GC that had interesting EIMS, but which did not correspond to the intended bis-TMS derivative (19, RMM = 356). Both new products had ions with  $m/z \geq 373$ . The latter had a base peak at  $m/z$  254, the mass of the cyclic bis-pyridyl compound, 16, but the higher-mass ions appeared to be genuine. The structure of these compounds was not deduced; they were quite unstable in solution and were not detectable after 40 minutes. However, when chlorotrimethylsilane was added to the remaining bulk of the reaction mixture which was then left overnight at  $20^\circ\text{C}$ , three major peaks were seen, eluting later in the GC than the starting material. These compounds had spectra that had not been seen before, all having base peaks at  $m/z$  178 and abundant ions at  $m/z$  73. The earlier-eluting compound had low-abundance ions at  $m/z$  357 and 358. The other two, which had similar retention times, eluted somewhat later and had low-abundance ions at  $m/z$  429. These higher mass peaks, only being present at the 1% level, might have gone unnoticed had it not been for a subsequent GC/MS analysis accidentally conducted at unusually high concentration. Under these conditions, in the regions of high concentration in each of the three GC peaks, self-chemical ionisation prevailed, and the three compounds had CIMS base peaks at  $m/z$  357,

429 and 429 respectively. These were believed to be attributed to compounds with the structures depicted in Scheme 5.9. In each case, it was the protonated form that gave the high mass ion. The EIMS molecular ion was of extremely low abundance.



Scheme 5.9. Possible structures of the TMS derivatives of 4,4'-(1,4-butanediyl)bispyridine (17)

The first-eluted compound was thought to be **19** (*i.e.* that shown in Scheme 5.9a). The later-eluting compounds may have been as shown in Scheme 5.9b and 5.9c. A further possibility was that the last-eluted compound was tetra- substituted (the MS was only scanned to 450 amu). Alternative structures can be drawn where there are two, three or four TMS groups bonded to the nitrogen atoms. It was possible that the initially-formed product was the nitrogen-bonded structure, perhaps being kinetically favoured, but that the thermodynamically more stable product ensued. One distinct difference between the EIMS of these and of related compounds was the presence of the base peak at  $m/z$  178. It appeared that the molecular ion split into two equal-size fragments following

dissociation at the CH<sub>2</sub>-CH<sub>2</sub> bond. This behaviour was dissimilar to the fragmentation process in **17**, in which the molecular ion was a major component of the EIMS and CH<sub>2</sub>-CH<sub>2</sub> bond dissociation did not occur to a great extent. Whether this was simply due to the presence of the TMS moiety adjacent to the CH group was not clear. On the other hand, the difference in EIMS behaviour may suggest a different position of substitution, such as in Scheme 5.9c.

The NMR spectrum of the isomer mixture described above was difficult to interpret. Reversed-phase HPLC failed to resolve the isomers seen in the mixture. The only compounds that were seen gave different EIMS, suggesting that the product isomers were either not eluted or had decomposed. While the TMS derivatives were not successfully isolated or characterised, there was sufficient evidence that, on the larger scale, the chlorosilane coupling reactions were more promising.

A further preparation using similar methods was carried out. The rate of lithiation was slow at -78°C (after 2.5 hours the mixture was deep orange but only 38% monolithiated and 7% dilithiated). After *ca.* 1 hour at 5°C it was 50% monolithiated and 30% dilithiated. Simultaneously it was noted that, compared with the peak area of ethylbenzene (present in the LDA solution and taken as being constant concentration), the total peak area for the three isotopic isomers of **17** had reduced to 17% of its original relative concentration. There was no obvious sign of products from this apparent decomposition. The addition of dichlorodimethylsilane failed to produce any new later-eluting components in the GC (or any compounds with EIMS corresponding to the desired cyclic product, **18**). Even after raising the temperature to 20°C and repeating the D<sub>2</sub>O test, the result still showed the presence of significant amounts of mono- and bisdeuterated **17** (50% and 20%), suggesting those proportions of mono- and dilithiated **17**. It was not established whether this

corresponded to the lithiated **17** not having reacted with the chlorosilane, or that whatever product was formed reacted with D<sub>2</sub>O to produce deuterated **17**.

As it appeared that there was still mono- and dilithiated **17** in the reaction mixture, further dichlorodimethylsilane was added, resulting in the formation of small amounts of two compounds that eluted later in the GC than the starting material. While the EIMS confirmed the presence of the pyridyl group in both new compounds, it was impossible to elucidate the structure further. There were no ions over  $m/z$  123, and no sign of the molecular ion expected from the desired product (**18**, RMM = 268). Mono- and dilithiated **17** still appeared to be present. From the remaining reaction mixture, the products were worked up to a brown oil, which, according to the GC/MS, showed the presence of earlier-eluting siloxanes (base peak having  $m/z$  73), a little **17**, and small amounts of the two components noted above. Because of the low concentration of these two compounds, the NMR was of no use in the analysis of this mixture, showing only the siloxanes that were to be expected from the large excess of chlorosilane used. In an attempt to prepare a better sample of the target compound, the preparation was repeated.

Working at a 3 times scale and adding the LDA to **17** at a higher temperature (0°C), a D<sub>2</sub>O test after one hour showed there to be molecular ions for **17** with  $m/z$  212, 213 and 214 in the ratio 12 : 35 : 53, inferring that **17** was mostly dilithiated. Small scale tests with (CH<sub>3</sub>)<sub>2</sub>SiCl<sub>2</sub>, and (CH<sub>3</sub>CH<sub>2</sub>)<sub>2</sub>NSi(CH<sub>3</sub>)<sub>3</sub> failed to provide evidence for the expected products (in the latter case, derivatives with fragments with  $m/z$  178 which might have corresponded to **19** or other compounds of the type shown in Scheme 5.9 were not seen). After addition of dichlorodimethylsilane to the bulk reaction mixture, GC/MS analysis of a sample (quenched with D<sub>2</sub>O, then extracted as usual), showed a product eluting later than the starting material. This had an EIMS almost identical to that previously seen in an earlier preparation (4-vinylpyridine and dichloromethylsilane added to sodium in THF), which

was believed to be **18**. The retention times differed, having been run under different GC conditions, but the eight most abundant ions in the EIMS matched extremely well. The EIMS corresponded well with the structure in Scheme 5.4b, the major fragments being shown in Scheme 5.5. According to the relative peak area, there was 15% of the amount of this product, **18** with respect to **17**. For reasons still not understood, on the basis of the D<sub>2</sub>O test, **17** still appeared to be present mostly as the dilithiated compound, to a slightly lesser extent as the monolithiated compound, and some unreacted **17**. One conclusion that must be considered from this and similar results is that the dilithiated **17** was formed, reacted to generate products (either those identified here or unknown compounds), which then decomposed (completely or partially) on addition of D<sub>2</sub>O to regenerate the bisdeuterated **17**, as shown in Scheme 5.3. On standing, the reaction mixture cleared, leaving a brown tarry residue and an orange-brown supernatant. Repeated analysis (D<sub>2</sub>O tests) showed that there was little and apparently decreasing amounts of **18** present in the supernatant. After boiling off the solvent (temperature up to 130°C), and dissolving the viscous brown residue, the D<sub>2</sub>O test and GC/MS revealed that the major two products were **17** and **18**, the latter approaching the concentration of **17**. This was the highest relative concentration of **18** observed to date in these experiments. Refluxing the residue in *o*-xylene (bp 144°C) for 15 minutes had a detrimental effect; the relative concentration of **18** had reduced to 25%. The concentration of nonlithiated **17** had increased to become equal to the sum of the mono- and dilithiated analogues. Although the *o*-xylene had been refluxed over, and distilled from sodium, water had clearly been introduced into the system. The extracted sample used for this analysis was stable for 20 minutes, but decomposed overnight. The remaining product solution separated into two layers overnight, the upper layer containing a higher ratio of product to starting material. Low pressure evaporation of solvent was extremely difficult, because of bumping, but *ca.* 5 ml of orange, fairly mobile liquid remained. For the first time, the ratio of **18** to **17** was greater than unity, although the

overall concentration, though not accurately quantified, appeared lower. A sample of **18** suitable for NMR analysis had still not been prepared.  $^1\text{H}$  NMR of the sample at this stage showed that it was contaminated with 5 moles of *o*-xylene. No *isopropylamine* was present. The  $^1\text{H}$  NMR was complicated by the presence of solvent peaks, but there appeared to be some evidence for a compound with pyridyl and alkyl proton signals consistent with the structure of **18**. However, there were a number of minor  $\text{SiCH}_3$  signals and it was difficult to confirm the presence of **18**. The  $^{29}\text{Si}$  NMR spectrum confirmed the mixture of silicon containing compounds, containing four signals from  $-21.65$  to  $8.79$  ppm.

Many attempts to remove **17** from **18** by extraction failed. On adding diethyl ether to the solution, some orange precipitate was formed. Trituration with ethyl acetate or with ethyl acetate/water (neutral or basified) mixtures produced solutions with low **18/17** ratios, according to the GC/MS. One sample that had been extracted using ethyl acetate/water was analysed by GC/MS soon after extraction and after 4 hours. The **18/17** ratio had dropped from 0.6:1 to 0.2:1. As before, the concentrations of these components were compared with that of ethylbenzene. It seemed fairly certain that a decrease of concentration of **18** was accompanied by an increase of concentration of **17**. There was no sign of other decomposition products.

Although these results were interesting, no further time was spent on the dimethyl compound, it being of no direct relevance as a chiral reagent precursor.

### 5.7 *Larger scale attempted preparation of 16*

Using the same procedure as above, on a similar scale (2 mmol), the diorganolithium salt of **17** was prepared ( $\text{D}_2\text{O}$  test result: 70% dilithiated and 23% monolithiated) at  $0^\circ\text{C}$ . After adding dichloromethylsilane at  $-78^\circ\text{C}$  the mixture was analysed by GC/MS ( $\text{D}_2\text{O}$  test), but no new peaks were apparent. After refluxing overnight, the GC/MS analysis was repeated,

but this time two samples were checked, one with the usual D<sub>2</sub>O test, the other without the D<sub>2</sub>O quench, and using oven-dried glassware; there were still no new peaks in the GC/MS, and no peaks with m/z 254. The mixture was evaporated under anhydrous conditions (oil pump) to yield a pale brown solid. Again the GC/MS (D<sub>2</sub>O test) showed no new peaks. The <sup>1</sup>H NMR provided some evidence for substitution in the pyridine ring. Signals for protons located at the C-2 and C-3 of the pyridyl group in **17** were usually observed at 8.45 and 7.06 ppm. In the spectrum of this residue, there was only one type of signal at 8.5 ppm, but 3 signals that appeared to be due to protons at C-3 (having shifts in the range 7.3 to 7.1, with integral ratios approximately 17 : 38 : 45). This was initially thought to have indicated the presence of a double bond at C-4 (or an isomer substituted at C-4), which would render the two C-3 protons inequivalent, but the chemical shifts suggested the preservation of aromaticity. Also, there was not the concomitant decrease in integral for the butyl chain proton adjacent to the ring.

The only <sup>1</sup>H signal which appeared to be due to silicon-containing compounds was that at 0.1 ppm, which was presumably a CH<sub>3</sub>-SiR<sup>1</sup>R<sup>2</sup>R<sup>3</sup>, where R<sup>n</sup> was not H (SiCH<sub>3</sub> signal was singlet) or Cl (δ<sub>H</sub> too low) R<sup>n</sup> could have been an alkoxy group. The integral of this signal was low compared with that of the pyridyl- containing compounds (1/3 mole of SiCH<sub>3</sub>). There may have been silicon products of the type CH<sub>3</sub>-SiHR<sup>1</sup>R<sup>2</sup> which were insoluble and not seen in the NMR spectrum, or possibly the SiH bond was broken in a hydrosilylation reaction (across a double bond in a non-aromatic rearranged form of the dilithium salt of **17**). Refluxing the mixture with *o*-xylene failed to produce the desired compound, or indeed any new compound, as far as could be established using GC/MS with the usual D<sub>2</sub>O test.

In an attempt to gain a better understanding of the nature of the products from this reaction, which may not have been apparent from the GC/MS analysis only, the reaction was

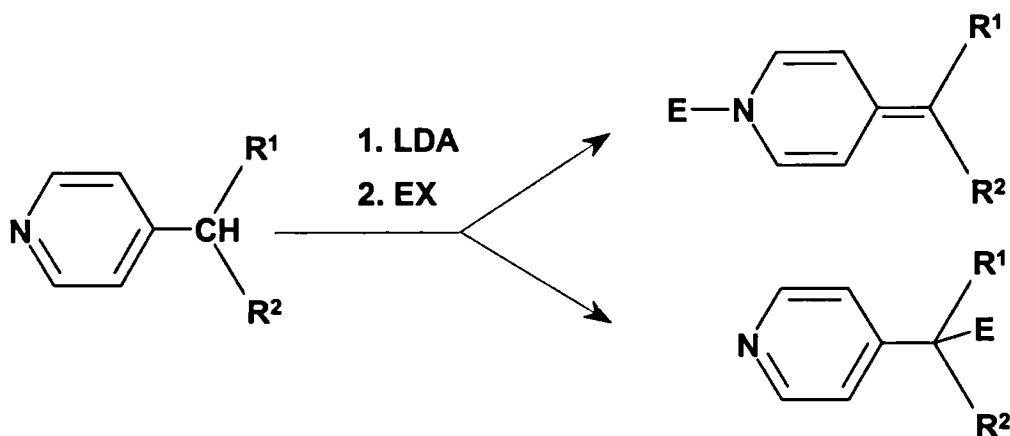


repeated in an NMR tube using THF- $d_8$  as solvent. **17** was dilithiated (confirmed by GC/MS  $D_2O$  test) and then dichloromethylsilane added. The GC/MS  $D_2O$  test was repeated, with no apparent change and no sign of any compound with  $m/z$  254 which might have corresponded to **16**. The  $^1H$  NMR spectrum was complicated by the presence of heptane, THF and ethylbenzene from the LDA reagent. However, there was no evidence for a  $SiCH_3H$  doublet and the pyridyl C-2 at 8.4ppm appeared as a multiplet. The  $^{29}Si$  spectrum contained five bands from 16.3 to -18.7 ppm. The products were clearly a mixture of silicon containing products, with no evidence for the desired compound, **16**.

#### 5.8 *Summary of work on attempted preparation of 1-methyl-2,5-di-(4-pyridyl)silacyclopentane (16)*

Only towards the end of this study, it became apparent that one of the target products, **18**, had only a limited stability in the solutions prepared for the main analytical technique, GC/MS. Nevertheless, this was still a useful measure of purity, since solutions were always analysed very soon after extraction, and **18** was shown to have a  $t_{1/2} \approx 4$  hours (although this would be very pH sensitive). The most significant problem, which was not appreciated in earlier work, was that **18** probably decomposed to produce **17**.

Because of the earlier problem with using an alkyllithium as a base in the reactions with **17**, the literature was consulted on compounds with the 4-methylpyridine (4-picoline) unit. This revealed some interesting and very relevant studies. In particular, Anders *et al*<sup>190</sup> showed that substituted 4-methylpyridines, of the type shown in Scheme 5.10, are normally substituted by the electrophile EX at the  $C_\alpha$  position, but depending on the nature of the substituents  $R^1$  and  $R^2$ , substitution may occur at N.



Scheme 5.10 Alternative positions of electrophilic substitution

When  $\text{EX} = (\text{CH}_3)_3\text{SiCl}$  and  $\text{R}^1 = \text{tosyl}$ ,  $\text{R}^2 = \text{phenyl}$ ; or  $\text{R}^1 = \text{N}(\text{CH}_3)_2$ ,  $\text{R}^2 = \text{H}$ , electrophilic attack was directed to N. This also occurred with some other electrophiles, for instance when  $\text{R}^1 = \text{R}^2 = \text{CH}_3$ . However, when  $\text{R}^1 = \text{R}^2 = \text{H}$  substitution at  $\text{C}_\alpha$  occurred. This behaviour was believed to be due to the position of initial substitution by lithium. Lithium was shown to be located at N and "direct" exchange of the lithium cation by the  $\text{Si}(\text{CH}_3)_3^-$  group led to the N- substituted product. Compound 17 had  $\text{R}^1 = \text{alkyl}$ ,  $\text{R}^2 = \text{H}$ , so might be expected to behave in either way, *i.e.* so that substitution by the  $\text{Si}(\text{CH}_3)_3^-$  group, might be at  $\text{C}_\alpha$  or at N. I had hoped that, should the N- substituted product have been formed, it may have converted to the aromatic  $\text{C}_\alpha$  substituted isomer on heating. The GC/MS provided no evidence for such a change.

Another feature of this paper was that the products of either type in Scheme 5.10 were found to be sensitive to moisture and had a tendency for thermal decomposition. Similar ease of hydrolysis of  $\text{C}_\alpha$  substituted 4-methylpyridines was reported by Eaborn and Shaw.<sup>186</sup> Anders *et al* reported the successful isolation of a TMS derivative from only one disubstituted 4-methylpyridine, *viz.* that having  $\text{R}^1 = \text{tosyl}$ ,  $\text{R}^2 = \text{phenyl}$ . Other  $\text{C}_\alpha$  substituted products were isolated (where  $\text{EX} = \text{TMS chloride}$ ,  $\text{R}^1 = \text{H}$  and  $\text{R}^2 = \text{Si}(\text{CH}_3)_3$ ,  $\text{OCH}_3$ , F, or Cl). These products were successfully extracted from ether/water mixtures.

Almost certainly, the problems of instability and decomposition of target compounds, or of unknown by-products, to produce **17** or deuterated analogues applied to the attempted preparations of all the compounds containing the 4-pyridyl-C-Si group, **16**, **18** and **19**.

If instability was the reason for the inability to repeat GC/MS analyses or to isolate product, the reagent (**16**) would be of no use as a reagent as proposed.

If any further work was considered in this area it should be noted that problems may arise when using the small-scale testing procedures described. The method of testing reaction mixtures by adding small samples to reagents, such as chlorosilanes, followed by quenching with D<sub>2</sub>O, then analysis by GC/MS was frequently a quick and easy means of examining the progress of the reaction. However, on two occasions different products were obtained when the chlorosilane reagents were added to the bulk reaction mixtures. This may well have been due to the increased difficulty of avoiding interference with extraneous water when working on the smaller scale.

Reaction monitoring by NMR was severely hampered by the presence of ethylbenzene, heptane and non-deuterated NMR solvent. Avoidance of these components in any future work would facilitate the determination of the position of electrophilic substitution.

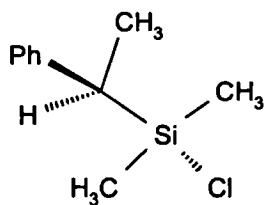
## CHAPTER 6

### CONCLUSIONS AND FURTHER WORK

#### 6.1 Evaluation of the preparation of reagents

The experiments described here were designed as a 'proof of principle' to assess the simplicity of formation of the chlorosilane reagents and to gauge the ease of discriminating between the diastereoisomeric products by NMR, GC or HPLC. The reagents were prepared as racemates and in many cases were used to derivatise compounds as racemates to evaluate the analytical technique.

##### 6.1.1 Preparation of 1-phenylethylchlorodimethylsilane (3)



**3**

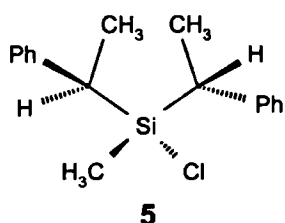
The preparation of **3** was simple, although the overall yield was reduced because that of the precursor silane **2** was low (27%). This was partly due to the formation of the Wurtz-type coupled product dimers, 2,3-diphenylbutane. Later work (preparation of **4**) showed that the proportion of dimeric impurities could be

reduced by placing the chlorosilane with the magnesium before the addition of (1-bromoethyl)benzene; the Grignard reagent is therefore generated in the presence of excess chlorosilane.

A useful extension of this work would be to prepare the homochiral precursor silane and hence homochiral **3**. Derivatisation of model alcohols would give predictable results, on the basis of results reported here. Preparation of the homochiral silane would rely on a Grignard or similar reaction proceeding with stereochemical integrity. With this reagent, in

the derivatisation of nucleophilic analytes, the mechanism of substitution of the chlorosilane (retention or inversion of configuration) would have no effect on the stereochemical outcome.

#### 6.1.2 Preparation of bis(1-phenylethyl)chloromethylsilane (5)

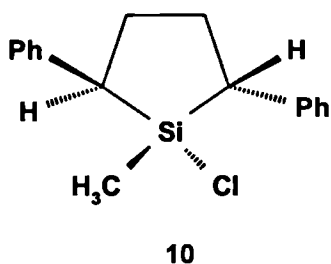


The precursor silane, bis(1-phenylethyl)methylsilane (4), was formed in reasonable (64%) yield. Formation of the Grignard reagent in the presence of dichloromethylsilane limited the amount of 2,3-diphenylbutane dimers to 20%. Distillation to

remove this impurity was difficult because of the ready solidification of the condensate such that the dimer content was only reduced to 14%.

The interpretation of derivatisation experiments was complicated by the presence of the two *meso*-isomeric impurities in the reagent. As with reagent 3, it would be possible to prepare the homochiral silane from homochiral starting materials and evaluate as discussed above.

#### 6.1.3 Preparation of 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10)



The preparation of the racemic silane precursor, 1-methyl-2,5-diphenylsilacyclopentane (6) was achieved successfully, but was problematic, due to the difficulty in trapping the dianion formed from styrene. This resulted in the

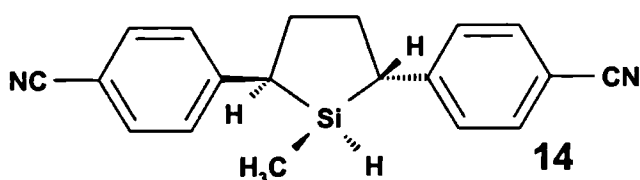
formation of polystyrene and silicon copolymers and a typical yield of only 8% of 6. A number of parameters were varied in an attempt to improve the yield, but to no avail. In particular, changing the order of addition had little effect: it had been hoped that addition of the styrene to a mixture of dichloromethylsilane and alkali metal would ensure a low concentration of styrene and minimise the polymerisation. Monitoring the reaction by

NMR was a particularly effective way of assessing the results of different reaction conditions, allowing a reasonable estimate of the yield without the need to work up every reaction mixture.

A further complication was the accompanying *meso*-isomers, but these were separated quite readily by normal-phase HPLC. Resolution of the enantiomers of **7** was achieved by HPLC, using a chiral stationary phase, Chiralcel OD, (cellulose tris(3,5-dimethylphenylcarbamate) coated on 5  $\mu$ m spherical silica). Circular dichroism spectroscopy was useful in characterising the enantiomers of **7**.

1-Chloro-1-methyl-2,5-diphenylsilacyclopentane **10** was readily prepared from the silane **7**, in many cases by direct chlorination in an NMR tube. After displacing excess chlorine with nitrogen, **10** could be used without further purification.

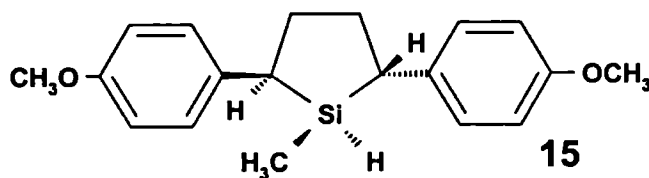
#### 6.1.4 Attempted preparation of 1-methyl-2,5-di-(4-cyanophenyl) silacyclopentane(**14**)



Whereas GC/MS and NMR provided good evidence for the formation of **6** in the previous

reaction, these techniques confirmed the failure of the preparation of **14**, with the major products being polymeric.

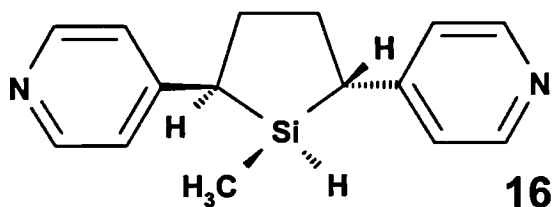
#### 6.1.5 Attempted preparation of 1-methyl-2,5-di-(4-methoxyphenyl) silacyclopentane (**15**)



For the same reasons that applied in the preparation of **14**, the formation of **15** was also considered to have

failed.

#### 6.1.6 Attempted preparation of 1-methyl-2,5-di-(4-pyridyl)silacyclopentane (16)



As in the above cases with 14 and 15, an analogue of styrene was dimerised, but cyclisation with a dichlorosilane failed to produce compound 16, as evidenced by

NMR or GC/MS. In this experiment however, the main identified product was 4,4'-(1,4-butanediyl)bispiridine (17).

Investigation of the reaction mixture showed the presence of the disubstituted organometallic precursor of 17, on the basis that this compound abstracted two deuterium atoms from D<sub>2</sub>O to form the 1,4-bisdeuterated isotopic isomer of 17.

In the expectation that polymeric by-products might be avoided by carrying out the preparation of 16 in two stages, 17 was prepared and isolated. The diorganolithium compound was prepared more successfully by adding lithium di-*iso*-propylamine than by using butyllithium, the latter reagent causing alkylation of the pyridyl groups.

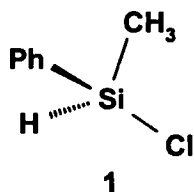
Addition of chlorosilanes (dichloromethylsilane, dichlorodimethylsilane, or chlorotrimethylsilane) occasionally gave evidence that the silicon-substituted compounds, including 16, had been formed. However, these compounds were impossible to isolate. It is likely that these compounds were formed but decomposed prior to analysis.

It appears that, because of its instability, 16 would always be difficult to prepare and would be useless as an analytical reagent.

## Evaluation of the reagents for chiral analysis

Chlorosilane reagents **1**, **3**, **5** and **10** were used in racemic form to derivatise the chiral alcohols 1-phenylethanol, 2-butanol and (1*R*, 2*S*, 5*R*)-menthol to produce the silyl ethers **1a-c**, **3a-c**, **5a-c** and **10a-c**, as shown in Scheme 4.9.

### 6.1.7 Chloromethylphenylsilane (**1**)

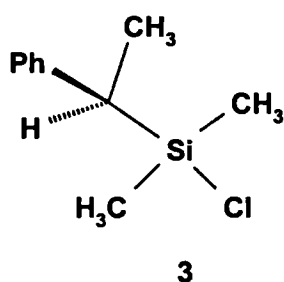


This reagent reacted rapidly with alcohols. The diastereoisomeric derivatives of **1a-c** were readily distinguished by NMR, but only **1a** and **1b** were separated by GC. The derivatives had poor hydrolytic

stability and were readily hydrolysed, even in normal-phase HPLC using specially dried solvents.

However, as was noted in the introduction, this compound is liable to racemise either before, during or after reaction and was not expected to be a useful reagent for chiral analysis.

### 6.1.8 1-Phenylethylchlorodimethylsilane (**3**)



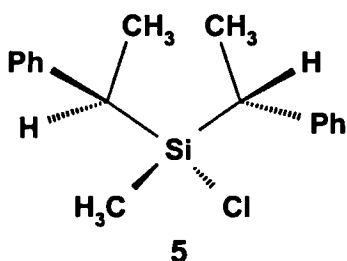
Reactions to produce **3a-c** were only attempted using stoichiometric proportions of reagents. Under these conditions the reaction was extremely slow, but proceeded quickly in the presence of base. The SiCH<sub>3</sub> signals in either the <sup>1</sup>H or the <sup>13</sup>C spectra of the diastereoisomeric derivatives were very readily

distinguished by NMR, although the presence of the two diastereotopic SiCH<sub>3</sub> groups complicated the spectrum when analysing mixtures of diastereoisomers. None of the diastereoisomers **3a-c** were resolved by GC. This was believed to be due to the conformational freedom possible in the molecule, reducing the potential for discriminatory adsorption on the stationary phase. Partial resolution was obtained by normal-phase HPLC



for the diastereoisomers of **3a** and **3b**, but not **3c**, although the resolution was inadequate for analytical work ( $R_s < 0.8$ ). Reversed-phase HPLC was not attempted, since it is often less effective in the resolution of diastereoisomers (because hydrogen bonding and other polar interactions are reduced in the presence of water).

*Bis(1-phenylethyl)chloromethylsilane (5)*

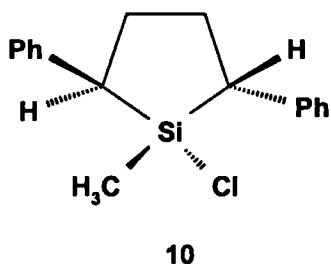


In the presence of base, **5** reacted readily to produce the silyl ethers **5a-c**. The diastereoisomeric derivatives were well distinguished by NMR, although the spectrum was complicated by the presence of the products of the *meso*-

isomers of **5**. In all the silyl ethers **5a-c** the diastereoisomers arising from the *meso*-isomers of **5** were well resolved by GC and by HPLC, but not the diastereoisomers arising from the enantiomers of **5**.

This reagent seemed to have less potential utility. Only if it could be prepared in homochiral form and, in particular, without the presence of the *meso*-isomers, might it be useful for NMR studies, but not for GC or HPLC.

*6.1.9 1-Chloro-1-methyl-2,5-diphenylsilacyclopentane (10)*



In the presence of base, **10** reacted readily to produce the silyl ethers **10a-c**. The diastereoisomeric derivatives were well distinguished by NMR, which was much simplified when the reagent was prepared from the

chromatographically purified chiral silane **7**. As with the derivatives of the acyclic analogue **5**, the products of the *meso*-isomers were well resolved by GC and by HPLC, but not those of the enantiomers of the reagent, except in the case of the derivative of menthol **10c**, which was extremely well separated by normal-phase HPLC.

## Overall assessment of the reagents for chiral analysis

Generally, the chlorosilanes reacted well with the alcohols used in this study to produce diastereoisomeric silyl ethers that, in all cases, could be distinguished by NMR. However, in the compounds that provided stable derivatives (3, 5 and 10) it appeared that, despite the chiral centres being in closest possible proximity for this type of derivative (*i.e.* reagent chiral centre being *adjacent to*, rather than *at* the silicon atom), chromatographic separations were inadequate for routine use as chiral derivatisation reagents. This lack of resolution could not simply be due to the distance between the chiral centres. Comparison with, for instance, the work of Rose and Rimmer, where the alkyl ethers had five bonds between chiral centres ( $-\text{CH}_2\text{-O-CH}_2\text{-O-}$ ) showed that GC resolution could be achieved with a considerable chain length between centres. It had also been considered that the lack of distinction between the silyl ether derivatives in this project might have been due to the increased conformational freedom arising from the high temperature necessary for elution of these particular derivatives. However, Rose and Rimmer's separations were successful at temperatures up to 200°C.

The possibility exists that the lack of separation in this work was simply due to the conformational freedom arising from the longer SiO bond. The reported poor separation of silyl ether diastereoisomers compared with equivalent alkyl ethers was noted in Section 1.2.5.2. However, the diastereoisomeric silyl acetals prepared by Kaye and Learmonth,<sup>43</sup> though only partially resolved, did show slight separation.

There are two possible reasons why the silyl ethers failed: either the silyl ether group itself adsorbed strongly with the stationary phase, so that other interactions in portions of the molecule that might be more discriminatory were overshadowed, or it is quite possible that the extra interactions possible in previous workers' derivatives improved the

discrimination. For instance, in the case of the alkyl ethers of Rose and Rimmer, many other interactions are possible with the additional functionality present.

The presence of the SiCH<sub>3</sub> group was helpful in the evaluation of the preparative reactions and as a diagnostic tool in the chiral analysis, giving a distinctive signal in the NMR and often providing molecular ions or characteristic fragments in the MS. However, while the GC/MS was very helpful for reaction monitoring, none of the reagents examined here gave adequate GC separations to be useful as chiral derivatisation reagents for GC.

It might be possible to prepare reagent **5** selectively to avoid the problem of the *meso*-isomers and then resolve the enantiomers, but this reagent did not seem to be of much value for chiral analysis. For liquid chromatographic work, reagent **10** had the advantage over **5** that the conformational constraints in the reagent molecule resulted in better diastereoisomeric separation. However, this was only demonstrated in the separation of menthol derivatives, but was expected to apply to similar secondary alcohols.

If an improved synthesis was found for the cyclic chlorosilane **10**, this reagent might be worth pursuing as a reagent for NMR, and also possibly for further HPLC studies.

Overall, from the point of view of the ease of preparation and also from the encouraging results obtained from reagent **3**, this or a related compound may have some future for NMR work. Some closely related compounds have been investigated by other workers, as discussed in Section 1.2.3.3.

## 6.2 Suggestions for further work

As concluded above, reagent **3** or a related compound might be the most promising direction for future research, some of these having been investigated by other workers. However, the cyclic compounds investigated here have some interesting properties.

Incidental to the main study of the reaction of chlorosilane **10** with alcohols was the observation that the *meso*-isomers of **10** reacted at a different rate compared with each other and the enantiomers of **10**. This behaviour was noted on a number of occasions, particularly when the reaction mixture was analysed early and frequently, being apparent in reactions carried out in the absence of base, where the reaction was slower. One proposal that has been suggested from this study was that the reaction proceeded *via* penta-coordination at silicon. The means of distinguishing the diastereoisomeric products (NMR or chromatographic retention time) could be used for any extension of this work. Either a mixture of the four stereoisomers discussed here, or a mixture of the two *meso* isomers might be useful in studying the mechanism of substitution at the silicon atom (inversion *vs.* retention).

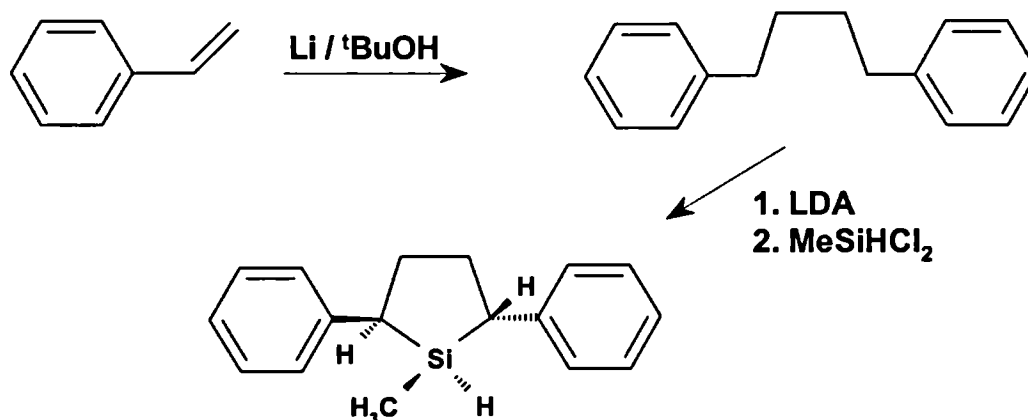
*Alternative routes to 1-methyl-2,5-diphenylsilacyclopentane (6)*

Alternative routes to this compound that were not attempted were:

- a) Cyclisation of the Grignard reagent prepared from 1,4-dibromo-1,4-diphenylbutane with dichloromethylsilane, although this route was not successful when attempted by Xu.<sup>162</sup>
- b) *Via* 1,4-diphenylbutane:

During the course of the work with the bispyridyl compounds, 4,4'-(1,4-butanediyl)bispyridine (**17**) was prepared, originally unintentionally. This was recognised as being a useful intermediate and was subsequently deliberately prepared as such. The advantage of carrying out the preparation in two stages was that the two essential reactions were performed independently, reducing the possibility of side reactions, and allowing

facile reaction monitoring. For the same reasons, an analogous route for the preparation of 1-methyl-2,5-diphenylsilacyclopentane (**6**) may be worth trying, as shown in Scheme 6.1.



Scheme 6.1 Possible alternative route to 1-methyl-2,5-diphenylsilacyclopentane (**6**)

This procedure would rely on two factors. Firstly, the efficient trapping of the dianionic intermediate by proton donation, as had clearly occurred in the preparation of (**17**). Tertiary butanol would be the obvious first choice as a source of protons. The competing process, *i.e.* polymerisation, should be less problematic here because styrene polymerises to a lesser extent than the pyridyl analogue, the rate constant for anionic polymerisation of styrene in THF being 25% that of 4-vinylpyridine.<sup>191</sup> Secondly, a suitable base is required to remove the benzylic protons to form the diorganometallic intermediate. The presence of this intermediate can be easily checked by the procedure of quenching with D<sub>2</sub>O, followed by GC/MS analysis. Once the presence of the diorganometallic intermediate has been verified, similar experiments to those performed on **17**, *i.e.* addition of chlorotrimethylsilane, and if this is successful, addition of dichlorodimethylsilane and dichloromethylsilane could easily be carried out and analysed.

The observation that 1,4-diphenylbutane (and 2,3-diphenylbutane) was present in older batches of LDA (supplied in solutions containing ethylbenzene) suggested a possible alternative preparation of 1,4-diphenylbutane. At the same time, the observation that **6** was

produced on addition of chlorotrimethylsilane suggested that the approach described above might be viable. (While this particular reaction could not be repeated and the mechanism, which must have involved some rearrangement, could not be elucidated, the involvement of a 1,4-dilithiated intermediate was still implied). However, the fact that ethylbenzene is used in the commercial LDA was not promising (because the coupled product and its dilithiated derivative would always interfere). Accordingly, a stronger base than LDA may be necessary, or LDA could be used at higher temperature to remove the benzylic protons.

The simplest assessment of the process would be to try to form the organolithium compound of ethylbenzene and test that with  $D_2O$ , and the chlorosilanes listed above.

Should this approach be successful, a related two-stage synthesis may be considered for the preparation of **14** and **15**.

#### *Further investigation of the use of 10 for NMR studies*

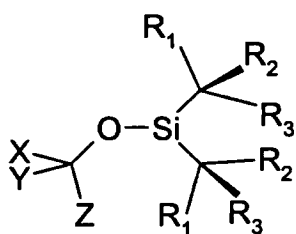
Although the chlorosilane, **10** produced diastereoisomeric silylethers that were generally unresolved by HPLC or GC, the results from the NMR were more promising. The  $SiCH_3$   $^1H$  signals from the silyl ethers were resolved and in a region of the spectrum which is typically clear (except for TMS and  $NaSi(CH_3)_3$ , etc). Thus **10** was a potential reagent for the determination of enantiomeric purity of alcohols and it was also possible that it could be used as a means to determine absolute configuration, in a similar way to that used with Mosher's acid.

Procedures described in this work could be used to test these possibilities, which have been used conveniently on a small scale. Each enantiomer of the silane, **7** can be resolved by HPLC. In an NMR tube, the homochiral silane can be chlorinated then reacted with a homochiral alcohol in  $CDCl_3$  solution. The  $^1H$  spectrum would show whether the single diastereoisomeric product was obtained.

If the procedure was successful, the work would be repeated with an alcohol over a range of enantiomeric purity, to determine the limits of detection and quantitation of the minor enantiomer. A study of different alcohols would show whether this approach had any utility in the assignment of absolute configuration of alcohols.

#### *Considerations for an improved chiral chlorosilane reagent*

Following this work, it seemed worth considering how a better reagent could be designed, that would provide improved diastereoisomeric discrimination in liquid or gas chromatography. It may be that there is inadequate proximity of the chiral centres to result in good chromatographic discrimination. The essential features of the structure of the



diastereoisomeric products prepared from the C<sub>2</sub>-symmetric type reagent are shown opposite. The main factors known to improve diastereoisomeric discrimination are the distance between chiral centres, the ability of those

groups in the vicinity of the chiral centres to be involved in chromatographic adsorption and the rigidity of that part of the molecule involved in chromatographic adsorption. It is not possible to reduce the number of bonds between the chiral centres with a compound of this design. The rigidity of the reagent molecule was increased in the cyclic structure **10**, with respect to the acyclic structure **5**, which had some effect on the resolution of the diastereoisomers, particularly in the HPLC of the menthol derivative, but offered no observable advantage in the GC. Including a double bond between the C<sub>3</sub> and C<sub>4</sub> atoms of the silacyclopentane ring would reduce the flexibility of the ring, but would only be expected to make a small difference, compared with the difference between the cyclic and acyclic compounds. Another possibility to improve this reagent would be to change the groups at the chiral centre, for instance, to include ester or amide groups in the place of the phenyl groups. A further means to enhance the discrimination would be to increase the

steric bulk in the region of the silylether bond, for instance by increasing the bulk at the face of the silacyclopentane ring. Of course, this would necessitate including similar groups on both faces of the ring to preserve the symmetry elements.

Whereas this sort of consideration might be worthwhile from an academic standpoint, it must be considered that, as a potential reagent increases in complexity, it would become extremely difficult to synthesize, unless a naturally occurring precursor was available. On cost grounds then, a more complex compound would rarely, if ever, be justified for use as a resolving agent, particularly if it could not easily be recycled.



## CHAPTER 7

### EXPERIMENTAL

#### 7.1 INSTRUMENTS

NMR spectra were recorded for solutions in  $\text{CDCl}_3$  on a JEOL JNM-EX400, unless stated otherwise.  $^1\text{H}$  data reported for isomer mixtures is in the format:  $\delta_{\text{H}}$ : *n.nn*, *p.pp*, .... (*qH*, *rm*, *assignment*), where *n.nn*, *p.pp*, .... is the chemical shift in ppm of signals for each diastereoisomer, *q* is the number of protons in **one** diastereoisomer, *r* is the number of signals, *m* is the multiplicity of each signal. All spectra were recorded on  $\text{CDCl}_3$  solutions, unless noted otherwise. TMS was sometimes used as chemical shift reference, but in many cases obscured  $\text{SiCH}_3$  signals from the sample. In such cases the  $\text{CHCl}_3$  signal ( $\delta_{\text{H}} = 7.26$  ppm) was used.

Except where noted otherwise, GC was recorded on a Varian 3400 gas chromatograph, which was coupled to a Finnigan MAT ITD mass spectrometer.

HPLC was carried out on with a Gilson model 303 pump with a Cecil Instruments model CE2112 UV detector and, for preparative work, a Gilson model 201 fraction collector. HPLC performed by Dr Stuart Laing (Glaxo Wellcome) (screening three chiral HPLC columns for resolution of 1-methyl-2,5-diphenylsilacyclopentane) was also carried out with a Gilson pump and UV detector.

Circular dichroism (CD) spectroscopy was performed with a Jasco J-720 spectrometer, by Ms Pat McDonough (Glaxo Wellcome).

Accurate mass was determined by high-resolution mass spectrometry on a Kratos MS80RFA instrument. Analysis was performed by direct insertion of 1  $\mu\text{l}$  of a chloroform

solution under EIMS conditions (ionisation energy 70 eV). Source temperature 250°C, probe temperature 40°C→350°C at 90°C/minute. Instrument resolution was 4000, sufficient to measure accurate masses to within 10 mmu of the expected values.

## 7.2 MATERIALS AND REAGENTS

Solvents for chemical synthesis were of general reagent grade, unless noted otherwise. Solvents for chromatography were HPLC grade. Reagents were of general reagent grade and obtained from Aldrich or other commercial sources. Chloromethylphenylsilane (1) was obtained from Fluka. Dichloromethylsilane and all alkali metals were obtained from Aldrich.

An HPLC silica column (250 × 4.6 mm 5 µm silica) was obtained from Jones Chromatography Ltd. A Chiralcel OD column (250 × 4.6 mm cellulose tris(3,5-dimethylphenylcarbamate) coated on 5 µm spherical silica (Daicel Chemical Industries)) was obtained from J T Baker Ltd. Other chiral HPLC columns (used at Glaxo Wellcome) were: Merck cellulose triacetate (200 × 4.6 mm) was obtained from BDH Ltd. and a ChiralPak AD column (250 × 4.6 mm, Daicel Chemical Industries) from J T Baker Ltd.

## 7.3 GENERAL PROCEDURES

### 7.3.1 *Drying of solvents, reagents and glassware.*

THF was the most commonly used reaction solvent. In all cases where water-sensitive reagents were used, THF was freshly distilled from sodium or potassium in the presence of benzophenone (the blue radical anion indicating that the THF was dry).

Alcohols used as reagents were dried by refluxing from magnesium.

Pyridine was dried by standing for >24 h over KOH pellets, then refluxing for 1 h over KOH, then distilling from KOH.

*n*-Hexane for chromatography was dried by distillation from sodium.

### 7.3.2 Instrumental conditions and analytical procedures

HPLC: All HPLC was performed with a mobile phase flow rate of 0.4 ml / min with UV detection at 254 nm., unless noted otherwise.

GC: All GC was performed under the following conditions, unless noted otherwise:

BP5 stationary phase, film thickness 0.25  $\mu\text{m}$ , 25m  $\times$  0.33 mm, detector temperature 250°C.

Method A: Splitless injection at 230°C. Temperature programme: 150 $\rightarrow$ 250°C at 10°C min<sup>-1</sup>.

Method B: Split injection at 230°C. Temperature programme: 60°C for 3 min; 60 $\rightarrow$ 250°C at 40°C min<sup>-1</sup>.

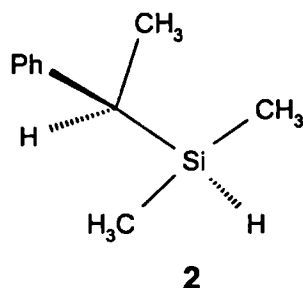
Method C: Splitless injection at 230°C. Temperature programme: 60 $\rightarrow$ 250°C at 10°C min<sup>-1</sup>.

Reporting of chromatographic data: all quantitative data was uncorrected for detection response factor, unless noted otherwise. All parameters are reported in accordance with the IUPAC nomenclature and recommendations.<sup>1</sup>

Samples of reaction mixtures for NMR analysis, which were usually water-sensitive, were normally handled entirely in oven-dried glassware. The typical procedure is as follows. 5-10 drops of reaction mixture is withdrawn from the reaction flask under nitrogen, added to 500  $\mu\text{l}$   $\text{CDCl}_3$ . Precipitation of salts often occurs, in which case the precipitate is spun down by centrifuge, avoiding introducing water from filter paper, *etc.* The NMR is recorded on the supernatant.

## 7.4 EXPERIMENTAL METHODS

### 7.4.1 1-Phenylethyldimethylsilane (2)



Magnesium turnings (1.44g, 59.2 mmol) were placed in dry diethyl ether (100 ml) with a crystal of iodine in a 100 ml round bottom flask fitted with a magnetic stirrer, condenser, nitrogen purge and bubbler. (1-Bromoethyl)benzene (10.0 g, 54.0 mmol) and dry diethyl ether (10 ml) were placed in a dropping funnel and a few drops of this solution added to the magnesium. After 0.5 h the reaction was initiated with a hot glass rod. The remaining reagent was diluted with diethyl ether (20 ml) and added over 0.5 h, maintaining a steady reflux. After 1 h there was still much magnesium present, so the mixture was refluxed for 1 h. The mixture was cooled in ice/water. Chlorodimethylsilane (3.0 ml, 27 mmol) in diethyl ether (15 ml) was added dropwise. The ice bath was removed and the mixture stirred overnight at 20°C. GC/MS analysis of the reaction mixture at this stage showed that there were more dimers than expected in the required. prod. The mixture was refluxed for 4 hours GC/MS analysis showed that the product / dimers ratio had dropped, suggesting that either the product had decomposed or that the dimer concentration had increased. Saturated  $\text{NH}_4\text{Cl}$  (50 ml) was added and the mixture refluxed to speed up the decomposition of excess magnesium. After cooling, the layers were separated, the aqueous layer being extracted with diethyl ether ( $2 \times 50$  ml). The combined ether layers were evaporated at 60°C / reduced pressure to yield a white crystalline solid which was distilled to give three fractions of colourless oil, designated F1, F2 and F3. Yields and GC/MS data for the crude input material and the higher-boiling undistilled residue are summarised in Tables 7.1 and 7.2.

sample	BP range / °C	pressure / mm Hg	yield / g
F1	45-50	0.04	0.197
F2	60	0.03	0.787
F3	60	0.05	0.228

Table 7.1 Distillation of 1-phenylethyldimethylsilane (2)

sample	GC peak retention time /s and compound identity					
	236 ethylbenzene	262 styrene	375 product	381 isomer <sup>1</sup> m/z 164	508 dimer	514 dimer
crude	<2	<2	35	<2	25	39
F1	4.0	4.5	85	2.6	<2	<2
F2	<2	<2	96	3.0	<2	<2
F3	<2	<2	94	4.7	<2	<2
residue	<2	<2	8.7	<2	38	54

Table 7.2 1-phenylethyldimethylsilane (2); GC / MS analytical data (expressed as % relative peak area / %) for crude, distillate fractions and residue.

Note: 1. peak at 381s. may be an isomer of 2, having a m/z of 164, a large M-15 peak, probably  $[\text{PhCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_2]^+$ , and a base peak with m/z 104.

Product analytical data:

i) GC/MS:

$t_R$ : 376 s: EIMS m/z: 164 ( $[\text{M}]^+$ , 36%), 121 (16), 105 (45), 104 (84), 103 (16), 79 (16), 77 (23), 59 ( $[\text{HSi}(\text{CH}_3)_2]^+$ , 100%), 43 (27).

ii) Accurate mass determination: Found: 164.10598 (Within 23 ppm of calculated value:  $\text{C}_{10}\text{H}_{16}\text{Si} = 164.10213$ ).

iii)  $^1\text{H}$  NMR:  $\delta_H$ : -0.02 (3H, d,  $\text{SiCH}_3$ ), 0.02 (3H, d,  $\text{SiCH}_3$ ), 1.39 (3H, d,  $\text{C-CH}_3$ ), 2.26 (1H, dq, CH), 3.83 (1H, dq, SiH), 7.06-7.26 (2H, m, Ar).

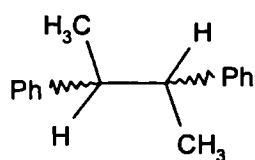
$^1\text{H}$ - $^1\text{H}$  COSY NMR (app159f2): cross-peaks confirmed  $\text{SiCH}_3$  to SiH and  $\text{CCH}_3$  to CH couplings.

$^{13}\text{C}$  NMR:  $\delta_C$ : -6.02 ( $\text{SiCH}_3$ ), -5.91 ( $\text{SiCH}_3$ ), 15.34 ( $\text{CCH}_3$ ), 27.69 (CH), 124.49, 126.92, 128.18, 145.50 (Ar).

$^1\text{H}$ - $^{13}\text{C}$  COSY NMR: cross-peaks correlated with above assignments.

$^{13}\text{C}$  DEPT NMR: peaks correlated with above assignments.

$^{29}\text{Si}$  NMR: dSi -6.10 ( $\text{Si}(\text{CH}_3)_2$ ).



Putative dimeric impurities analytical data, with probable structure shown alongside:

i) GC/MS:

$t_R$ : 508 s: EIMS  $m/z$ : 106 (7%), 105 (100), 104 (29), 103 (14), 79 (19), 78 (8), 77 (23), 51 (15), 39 (8).

$t_R$ : 514 s: EIMS  $m/z$ : 106 (7%), 105 (100), 104 (25), 103 (13), 79 (17), 78 (8), 77 (22), 51 (11), 39 (6).

ii)  $^1\text{H}$  NMR:

$\delta_H$ : 1.02 and 1.27 (6H, 2d,  $\text{CH}_3\text{CH}$  of 2 diasts), 2.79 and 2.93 (2H, 2dq,  $\text{CH}_3\text{CHCH}$  of 2 diasts), 6.99-7.31 (10H, m, Ar of 2 diasts). Cpw. *lit.*<sup>164</sup> (*RS,RS*)-2,3-diphenylbutane,  $\delta_H$ : 1.03 (6H, d,  $\text{CH}_3\text{CH}$ ), 2.75 (2H, m,  $\text{CH}_3\text{CHCH}$ ), 7.24 (10H, m, Ar). (*RR,SS*)-2,3-diphenylbutane,  $\delta_H$ : 1.17 (6H, d,  $\text{CH}_3\text{CH}$ ), 2.76 (2H, m,  $\text{CH}_3\text{CHCH}$ ), 7.24 (10H, m, Ar)

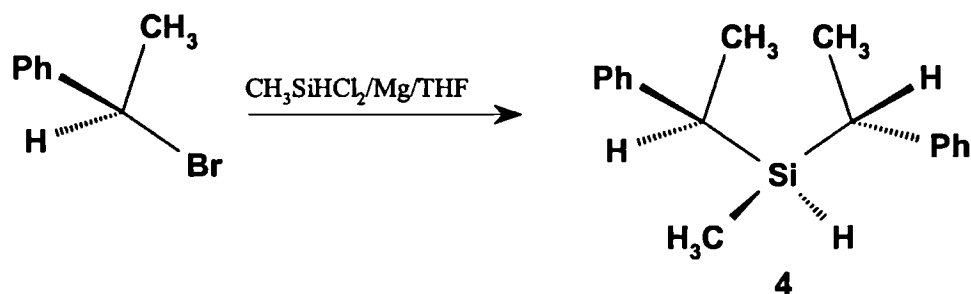
#### 7.4.2 1-Phenylethylchlorodimethylsilane (3)

All glassware was oven-dried before use. The combined 1-phenylethyldimethylsilane fractions (1.212 g, 7.39 mmol) were placed in a 10 mm NMR tube with  $\text{CCl}_4$  (8 ml, degassed by 20 min reflux) and chilled in an ice/water bath.  $\text{Cl}_2$  was bubbled through the solution, the NMR being checked frequently to avoid over-chlorination (disappearance of SiH band at 3.83 ppm). The final solution was transferred to a 50 ml flask containing antibumping granules, glass wool and a magnetic stirrer. Most of the solvent was removed under vacuum at 20°C and the product distilled to give the following fractions: 160f1 (52-53°C, 0.03 mm Hg, 1.09 g) and 160f2 (55-60°C, 0.015 mm Hg, 0.08 g), both colourless liquids, 80.3% th.

$^1\text{H}$  NMR:  $\delta_H$ : 0.31 (3H, s,  $\text{SiCH}_3$ ), 0.33 (3H, s,  $\text{SiCH}_3$ ), 1.46 (3H, s,  $\text{CCH}_3$ ), 2.42 (1H, q, CH), 7.1-7.2 (3H, m, Ar), 7.2-7.3 (2H, m, Ar).

The spectrum showed only very low impurity levels; product > 95% pure. No further analysis on this product.

#### 7.4.3 Preparation of bis(1-phenylethyl)methylsilane (4)



All glassware was oven-dried and purged with dry nitrogen before and during use. Dichloromethylsilane (3.80 ml, 4.20 g, 36.5 mmol), and magnesium turnings (2.02 g, 83.1 mmol) were placed in dry THF (10 ml) with a crystal of iodine in a 100 ml round bottom flask fitted with a magnetic stirrer, dropping funnel, condenser, nitrogen purge and bubbler. (1-Bromoethyl)benzene (13.51 g, 73.0 mmol) was placed in a dropping funnel and a few drops added to the flask. The mixture was heated to start the reaction, then the remaining alkyl bromide, mixed with dry THF (20 ml) was added at a sufficient rate to maintain reflux. The mixture was then refluxed for 2 hours, by which time very little magnesium remained.

1M HCl was added to decompose the excess magnesium. Excess HCl was removed by adding NaHCO<sub>3</sub>. Solvent was evaporated from the mixture, which was then extracted with diethyl ether / H<sub>2</sub>O (1:1 v/v, 3 × 100 ml), washed with H<sub>2</sub>O (2 × 25 ml), then dried with MgSO<sub>4</sub>. The extract was evaporated at 60°C / reduced pressure to yield a colourless oil.

GC: *t<sub>R</sub>*/s (relative peak area): 514 (9.3%), 519 (10.6%) and 572 (80% product), indicated the presence of 20% dimeric impurities.

The oil was distilled, using normal distillation equipment, but without condenser to avoid premature solidification, to give three fractions of colourless oil, designated F1, F2 and F3. Yields and boiling ranges are summarised in Table 3.

sample	BP range / °C	pressure / mm Hg	yield / g
F1	110-112	0.005	3.90
F2	110-112	0.005	1.88
F3	114-116	0.005	0.12

Table 7.3 Distillation of bis(1-phenylethyl)methylsilane (4)

Total product = 5.90g, 64% th.

GC (method B): Fraction F1 and F2 both had major product peaks at 570s and total dimer (508s and 513s) content = 25% and 14% respectively:

$t_R$ : 570s, EIMS  $m/z$  254: ( $M^{+}$ , 4%), 149 ( $[\text{PhCHCH}_3\text{SiHCH}_3]^+$ , 85), 122 (15), 121 (100), 105 (31), 79 (16), 77 (23), 43 (24).

$t_R$ : 508 and 513s, EIMS  $m/z$ : 106 (8%), 105 (100), 104 (27), 103 (13), 79 (22), 77 (22), 51 (12), 39 (7).

Slower gradient GC: (60°C for 3 min; 60→250°C at 10°C min<sup>-1</sup>): 3 peaks, only partially resolved:

$t_R$ /s: 1201, 1204, 1206, having peak area ratios approximately 1:2:1. The EIMS of each isomer was identical to that of the mixture, the molecular formula of which was confirmed by high resolution EIMS.

Accurate mass determination: Found: 254.15761 (Within 34 ppm of calculated value:  $\text{C}_{17}\text{H}_{22}\text{Si}$  = 254.14908).

The <sup>1</sup>H NMR spectrum was complicated by the existence of the product in three diastereoisomeric forms, the SiCH<sub>3</sub> signals at -0.26, -0.14, and 0.03 in the ratio 3 : 5 : 2. Chemical shifts and assignments are given in Table 7.4.

*Attempted resolution of diastereoisomers of bis(1-phenylethyl)methylsilane by HPLC:*

Bis(1-phenylethyl)methylsilane was injected onto a column of 250 × 4.6 mm 5 μm silica and eluted with neat hexane at 0.4 ml/min. Only one peak was produced, eluting immediately after the column dead volume; this was confirmed as being bis(1-phenylethyl)methylsilane by GC/MS (GC method B,  $t_R$ : 567s; EIMS  $m/z$ : 254 ( $M^{+}$ , 4%), 149 (87%), 121 (100%).

Bis(1-phenylethyl)methylsilane was injected onto a Chiralcel OD column, with a mobile phase of neat *n*-hexane, resulting in a peak evidently comprising at least five components,



all of which were only partially resolved. From 18 repeated injections onto the column, fractions were collected corresponding to these five components, having  $t_R$ : 12.9, 13.4, 13.7, 14.3, 15.1 min. These fractions were evaporated and analysed by GC/MS (Method B) and  $^1\text{H}$  NMR. The NMR data and assignments for the resolved stereoisomers of bis(1-phenylethyl)methylsilane (**4**) are given in Table 7.4.

Fraction 1: GC: One peak,  $t_R$ : 509 s, EIMS  $m/z$ : 105 ( $[\text{PhCHCH}_3]^+$ , 100%), 104 (27), 79 (22), 77 (25). Corresponded to one diastereoisomer of  $\text{PhCH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ .

$^1\text{H}$  NMR  $\delta_H$ : 1.02 (6H, d,  $\text{CH}_3\text{CH}$ ), 2.79 (2H, m,  $\text{CH}_3\text{CHCH}$ ), 7.04-7.26 (10H, m, Ar). (*RS,RS*)-2,3-diphenylbutane (literature assignments above).

Fraction 2: GC: Two major peaks:

$t_R/s$ : 561 (*ca.* 60% by peak area), and 563 (*ca.* 40% by peak area), both components having identical mass spectra: EIMS  $m/z$ : 254 ( $M^+$ , 4%), 149 (98), 121 (100), 105 (40), 43 (31).

Fraction 3: GC: One peak,  $t_R$ : 568 s, EIMS  $m/z$ : 254 ( $M^+$ , 4%), 149 (98), 121 (100), 105 (40), 77 (22), 43 (33).

Fraction 4: GC: One peak,  $t_R$ : 562 s, EIMS  $m/z$ : 254 ( $M^+$ , 4%), 149 (100), 121 (99), 105 (35), 43 (29).

Fraction 5: GC: Two major peaks:

$t_R/s$ : 504 (*ca.* 26% by peak area), EIMS  $m/z$ : 105 ( $[\text{PhCHCH}_3]^+$  100%), 104 (28), 79 (23), 77 (24). Corresponds to one diastereoisomer of  $\text{PhCH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ .

$t_R/s$ : 562 (*ca.* 74% by peak area), EIMS  $m/z$ : 254 ( $M^+$ , 3%), 149 (75), 121 (100), 105 (37), 43 (28).

$^1\text{H}$  NMR: Weak spectrum from minor component included  $\delta_H$ : 1.28 (6H, d,  $\text{CH}_3\text{CH}$ ), corresponding to (*RR,SS*)-2,3-diphenylbutane.

GC/MS analysis of stereoisomers of **4** at reduced thermal gradient (2°C/min):

Fraction 2: GC: Two peaks (mostly resolved):  $t_R$ /s: 646, 652

Fraction 4: GC: One peak,  $t_R$ /s: 649

sample	$\delta_H$ / ppm				Aromatic (m)	
	SiCH <sub>3</sub> (d)	SiH (dq)	CCH <sub>3</sub> (d)	CH (dq)		
input (mixture)	-0.26	3.79	1.39	2.28	7.00-7.12,	7.22-7.31
	-0.14	3.76	1.32, 1.35	2.34, 2.24	7.00-7.12,	7.22-7.31
	0.03	3.74	1.29	2.21	7.00-7.12,	7.22-7.31
(meso #1)	-0.26	3.79	1.40	2.28	7.03-7.12,	7.22-7.27
fraction 2 (meso #2)	0.04	3.74	1.30	2.21	7.03-7.12,	7.22-7.27
	-0.26	3.79	1.40	2.28	7.02-7.13,	7.21-7.28
	-0.14	3.76	1.34, 1.36	2.34, 2.24	7.02-7.13,	7.21-7.28
fraction 3 (mixture)	0.03	3.74	1.30	2.21	7.02-7.13,	7.21-7.28
			1.34	2.34		
	-0.14	3.76			7.02-7.13,	7.21-7.28
fraction 4 (enantio #1)			1.36	2.24		
			1.34	2.34		
	-0.14	3.76			7.02-7.13,	7.21-7.29
fraction 5 (enantio #2)			1.35	2.24		

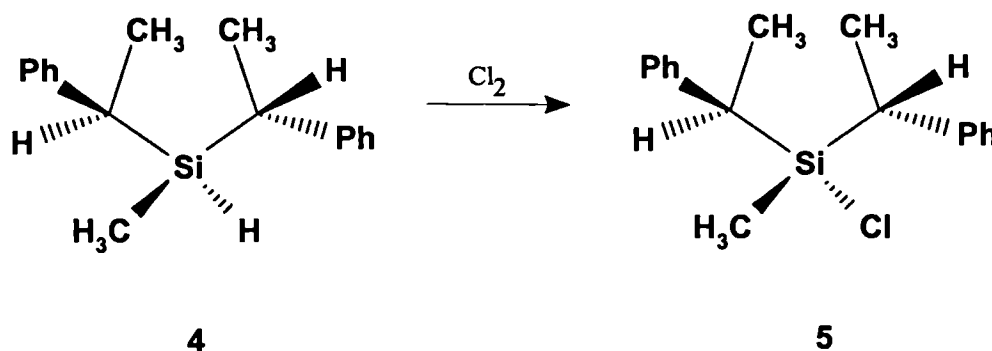
Table 7.4  $^1\text{H}$  NMR data from sample input to chiral HPLC and column fractions 2-5:

*Further NMR data (on unresolved isomer mixture)*

$^{13}\text{C}$  NMR spectrum: (all isomers),  $\delta_C$ : -10.08, -9.73, -9.20 (SiCH<sub>3</sub>), 15.51 (sl. br.), 16.51, 16.68 (CCH<sub>3</sub>), 25.62, 25.70, 25.88, 26.13 (CH), 124.67-128.29 (Ar), 145.17-146.43 (Ar C-1).

All  $^1\text{H}$  and  $^{13}\text{C}$  data was correlated by  $^{13}\text{C}$ - $^1\text{H}$  COSY. The SiCH<sub>3</sub>  $^1\text{H}$  and  $^{13}\text{C}$  shifts were correlated in inverse order of shift (e.g. isomer with highest  $\delta_H$  had lowest  $\delta_C$ ).

#### 7.4.4 Preparation of bis(1-phenylethyl)chloromethylsilane (5)



All glassware was oven-dried before use. The second fraction of bis(1-phenylethyl)-methylsilane (1.88 g, 7.40 mmol) was placed in a 10mm<sup>1</sup>NMR tube with CCl<sub>4</sub> (8 ml, degassed by 20 min reflux) and chilled in an ice/water bath. Cl<sub>2</sub> was bubbled through the solution, the NMR being checked frequently to avoid over-chlorination (disappearance of SiH bands at 3.7 ppm). The final solution was transferred to a 50 ml flask containing antibumping granules, glass wool and a magnetic stirrer. Most of the solvent was removed under vacuum at 20°C and the product distilled to give the following fractions: F1 (95-97°C, 0.0015 mm Hg, 0.134 g), F2 (97-102°C, 0.0015 mm Hg, 1.169 g), and F3 (102-105°C, 0.0015 mm Hg, 0.053 g), all colourless liquids, 63.5% th.

<sup>1</sup>H NMR of major fraction:  $\delta_{\text{H}}$ : 0.06, 0.17, and 0.35 (in ratio 3 : 5 : 2; 3H, 3s, SiCH<sub>3</sub> of 3 diasts), 1.33-1.46 (6H, m, CCH<sub>3</sub>), 2.33-2.41 (2H, 2q, CH), 7.02-7.26 (3H, m, Ar), 7.2-7.3 (2H, m, Ar).

Also evidence for *ca.* 11% residual PhCH(CH<sub>3</sub>)CH(CH)Ph diastereoisomers,  $\delta_{\text{H}}$ : 1.01 and 1.27 (3H, 2d, CH<sub>3</sub>), 2.78 and 2.92 (1H, dq, CH), aromatic signals in same region as product.

Otherwise there was only very low impurity levels; product *ca.* 90% pure. No further analysis on this product.

#### 7.4.5 *1-Methyl-2,5-diphenylsilacyclopentane (6)*

THF was freshly distilled from sodium prior to use as solvent and for washing the lithium. A mixture of dichloromethylsilane (15 ml, 0.14 mol) and lithium shot (2.8 g, 0.4 mol) in THF (50 ml) was chilled below 0°C in a flask flushed with N<sub>2</sub>. Styrene (33 ml, 0.29 mol) in THF (50 ml) was let into the flask via a pressure-equalising dropping funnel over 40 minutes so that the temperature did not exceed 0°C. The reaction was allowed to continue at 15°C, under a positive pressure of nitrogen. The reaction was monitored by GC, with a BP5 stationary phase, 25m × 0.33 mm, splitless injection at 225°C and detector at 250°C. The column temperature was raised from 60°C to 250°C at 5°C min<sup>-1</sup>.

After 50 h the reaction mixture still contained some styrene, and so a further portion of dichloromethylsilane (4.5 ml, 0.04 mol) was added to complete the reaction. After 80 h the reaction mixture was filtered to yield a thick syrup.

The product/polystyrene ratio was estimated by  $^1\text{H}$  NMR spectroscopy to be ca. 1:40 (polystyrene expressed as monomer). NMR showed that there was little styrene present. The product was separated by adding methanol (50 ml) to a well stirred solution of the crude product in chloroform (40 ml).

The supernatant was decanted from the white tarry precipitate and evaporated at  $60^\circ\text{C}$  under reduced pressure to yield a thick yellow gum (3.2g, 8.8%).

GC showed that the product was impure, but comparison with NMR data indicated that the impurity level was grossly underestimated by GC, probably due to the presence of higher molecular weight impurities that were not eluted from the GC column.

NMR spectra showed that the product was impure but included  $\delta_{\text{H}}$  (uncor.): 0.0 (3 H, d,  $\text{SiCH}_3$ ), 1.5-3.0 (6 H, m, CH,  $\text{CH}_2$ ), 4.1 (1 H, m, SiH), 7.0-7.4 (10 H, m, Ar).

Two further preparations of **6** gave yields of 2.5g and 3.0g crude material (6.9 and 8.3% th.). These two crude batches of **6** were combined with the first (totalling 8.7 g) and distilled at 0.08 mm Hg to yield six fractions as shown in Table 3.1 (Chapter 3). The total yield of **6** was 3.9g (3.6% overall th.) and the yield of the most pure fraction (#3) was 0.8g (0.7% overall th.)

Analytical data on fraction 3:

$^1\text{H}$  NMR:  $\delta_{\text{H}}$ : -0.1 (3 H, d,  $\text{CH}_3$ ), 1.9 (2 H, m,  $\text{CH}_2$ ), 2.4 (3 H, m, CH,  $\text{CH}_2$ ), 2.9 (1 H, m, CH), 4.1 (1 H, m, SiH), 7.2-7.4 (10 H, m, Ar).  $\text{SiCH}_3$  isomer signals  $\delta_{\text{H}}$ : -0.51, -0.01, 0.40 in a ratio of 7 : 81 : 11.

$^{13}\text{C}$  NMR:  $\delta_{\text{C}}$ : -6.6 ( $\text{SiCH}_3$ ), 32.6 ( $\text{CH}_2$ ), 33.4 (CH), 33.6 ( $\text{CH}_2$ ), 36.5 (CH), 124.2, 124.5, 126.5, 126.9, 127.2 (Ar), 143.2, 144.0, (*ipso*-Ar).

Further NMR data on the resolved diastereoisomers is reported later.

Accurate mass determination: Found: 252.13137 (Within 8 ppm of calculated value:  $C_{17}H_{20}Si = 252.1329$ ).

GC/MS recorded under various conditions:

Major peak had  $t_R$  / s: 463 (method A), 1015 (GC method C), 627 (method B). The best separation of isomeric product peaks was achieved with a temperature programme: 80°C → 180°C at 20°C / min, 180°C → 200°C at 3°C / min, from which the following data were obtained.

GC/MS: 3 major GC peaks:

$t_R$  /s: 716, 735 and 740; (with peak area ratio 12 : 16 : 72), 3 components with indistinguishable mass spectra: EIMS  $m/z$ : 252 ( $M^+$ , 72%), 147 (25), 117 (100), 105 (32), 104 (34), 91 (38), 78 (32), 43 (47).

In some batches of **6** an impurity was seen by GC/MS that eluted at 849 s (GC method C), having 7% of the area of the product isomers; EIMS  $m/z$ : 210 ( $M^+$ , 24%), 104 (16), 92 (48), 91 (100), 77 (11), 65 (32), 51 (10), 50 (11).

#### 7.4.6 *Resolution of diastereoisomers and enantiomers of 1-methyl-2,5-diphenylsilacyclopentane (7, 8 and 6)*

##### 7.4.6.1 *Normal-phase HPLC separation of diastereoisomers:*

The sample of **6** containing isomeric impurities was injected onto a silica column with a mobile phase of  $CH_2Cl_2$  / n-hexane (0.4 % v/v), separating four components, having  $t_R$ /min: 4.94, 5.04, 5.48, 5.88.

From  $23 \times 15 \mu l$  repeated injections, each of 1.5 mg sample onto the column, fractions were collected corresponding to these four components. These fractions were evaporated and analysed by GC/MS (Method B) and NMR. The input mixture and the fractions were also analysed under the optimised GC conditions noted above, as summarised in Table 7.6.

Fraction #	HPLC $t_R$ / min	GC $t_R$ / s	purity by GC/MS
Fraction 1	4.94	716	9% impurity of Ph(CH <sub>2</sub> ) <sub>4</sub> Ph 0% other isomers
Fraction 2	5.04	497 716	26% impurity of Ph(CH <sub>2</sub> ) <sub>4</sub> Ph 6% 'fraction 3' isomeric impurity
Fraction 3	5.48	740	100% pure isomer
Fraction 4	5.88	735	21% 'fraction 3' isomeric impurity

Table 7.6 Analysis of HPLC fractions by GC/MS

*NMR data (CHCl<sub>3</sub> ref.):*

Being a mixture, fraction 2 was not analysed further.

Fraction 3 (compound 7):  $\delta_H$ : -0.01 (3 H, d $\beta$ , SiCH<sub>3</sub>), 1.88-1.96 (2 H, m, CH<sub>2</sub>), 2.40-2.46 (3 H, m, CH+CH<sub>2</sub>), 2.85 (1 H, m, CH), 4.07 (1 H, m, SiH), 7.09-7.31 (10 H, m, Ar).

<sup>1</sup>H-<sup>1</sup>H COSY: Coupling correlations were observed between the protons at  $\delta_H$ /ppm: -0.01 and 4.07, 1.9 and 2.4, 1.9 and 2.9, 2.4 and 2.9, 2.4 and 4.1, 2.9 and 4.1.

<sup>13</sup>C NMR:  $\delta_C$ : -6.81 (SiCH<sub>3</sub>), 32.89 (CH<sub>2</sub>), 33.68 (CH), 33.88 (CH<sub>2</sub>), 36.73 (CH), 124.35, 124.59, 127.00, 127.05, 128.33, 128.46 (2 × Ph, C-(2-6)), 143.48 and 144.36, (2 × Ph, C-1).

DEPT spectrum identified <sup>13</sup>C signals with  $\delta_C$ : 32.89, 33.88 = CH<sub>2</sub>, 33.68, 36.73 = CH.

<sup>13</sup>C-<sup>1</sup>H COSY NMR: Coupling correlations were observed between the carbon nuclei and protons at  $\delta_C$  and  $\delta_H$ /ppm: -6.81 and -0.01; 32.89 and 1.9 and 2.4; 33.68 and 2.9; 33.88 and 1.9 and 2.4; 36.73 and 2.4; and also between the aromatic signals (*i.e.* 124.35 to 128.46 and 7.1 to 7.3).

Fraction 1 (compound 8):  $\delta_H$ : -0.51 (3 H, d, SiCH<sub>3</sub>), 2.20 (2 H, m, CH<sub>2</sub>), 2.29 (2 H, m, CH<sub>2</sub>), 2.85 (2 H, m, CH), 4.36 (1 H, q, SiH), 7.05-7.27 (10 H, m, Ar).

$^1\text{H}$ - $^1\text{H}$  COSY: Coupling correlations were observed between the protons at  $\delta_{\text{H}}$ /ppm: -0.51 and 4.36, 2.20 and 2.29, 2.20 and 2.85, 2.29 and 2.85.

Fraction 4 (compound 9):  $\delta_{\text{H}}$ : 0.40 (3 H, d,  $\text{SiCH}_3$ ), 2.25 (2 H, m,  $\text{CH}_2$ ), 2.32 (2 H, m,  $\text{CH}_2$ ), 2.53 (2 H, m, CH), 3.86 (1 H, m, SiH), 7.09-7.31 (10 H, m, Ar). This fraction contained a small impurity of 7, in accord with GC/MS result.

$^1\text{H}$ - $^1\text{H}$  COSY: Coupling correlations were observed between the protons at  $\delta_{\text{H}}$ /ppm: 0.40 and 3.86, 2.25 and 2.32, 2.25 and 2.53, 2.32 and 2.53, 2.53 and 3.86.

$^{13}\text{C}$  NMR:  $\delta_{\text{C}}$ : -5.33 ( $\text{SiCH}_3$ ), 33.86 ( $\text{CH}_2$ ), 34.97 (CH), 124.33 (Ph, C-4), 126.67 (Ph, C-3), 128.50, (Ph, C-2), 145.27, (Ph, C-1).

$^1\text{H}$ - $^{13}\text{C}$  COSY NMR: Coupling correlations were observed between the carbon atoms and protons at  $\delta_{\text{H}}$ /ppm: -5.33 and 0.40; 33.86 and both 2.25 and 2.32; 34.97 and 2.53; 124.33 and 7.11; 126.67 and 7.20; 128.50 and 7.29.

DEPT spectrum identified  $^{13}\text{C}$  signals: 33.86 =  $\text{CH}_2$ ; 145.27 = C-1

#### *Comparison of $^{13}\text{C}$ - $^1\text{H}$ COSY spectra of the three diastereoisomers*

The  $^{13}\text{C}$ - $^1\text{H}$  correlation spectra of a typical diastereoisomer mixture showed coupling correlations between the carbon nuclei and protons at  $\delta_{\text{C}}$  and  $\delta_{\text{H}}$ /ppm: -8.66 and -0.51, -6.81 and -0.01, 0.40 and -5.33.

#### *NMR analysis of fractions from other chromatographic separations ( $\text{CHCl}_3$ , ref.):*

At low loadings, the second HPLC fraction contained an impurity (up to 46% by GC peak area) which gave NMR signals corresponding to  $\text{Ph}(\text{CH}_2)_4\text{Ph}$ :  $\delta_{\text{H}}$ : 1.67 (4 H, m,  $\text{CH}_2$ ), 2.64 (4 H, m,  $\text{CH}_2$ ), 7.16-7.20 (10 H, m, Ar).

#### **7.4.6.2** *HPLC separation of enantiomers:*

Racemic 7 was injected onto each of three HPLC phases in an attempt to resolve the enantiomers: Cellulose triacetate (mobile phase 100% ethanol), and ChiralPak AD

(amylose tris(3,5-dimethylphenylcarbamate) coated on 5  $\mu\text{m}$  spherical silica, mobile phase 10% propan-2-ol in *n*-heptane), were unable to effect the resolution.

Racemic **7** was injected onto a Chiralcel OD column (250  $\times$  4.6 mm) with a mobile phase of *n*-heptane, flow rate 0.4 ml/min, separating two components,  $t_{\text{R}}$ : 10.36 and 13.29 min ( $\alpha = 1.40$ ,  $R_{\text{s}} = 3.46$ ). The loading was increased to 10  $\mu\text{l}$  of *ca.* 10 mg/ml solution for small scale preparative chromatography, with a mobile phase of *n*-hexane, giving  $t_{\text{R}}$ : 18.0 and 21.7 min. From repeated injections onto the column, the pooled fractions were collected, evaporated and analysed by GC/MS (Method B), NMR, UV and CD.

GC/MS: The two products from the initial small-scale preparative chiral HPLC had the same retention time (627 s) and had no impurities > 1%. The EIMS from each were indistinguishable and corresponded to that of the input material.

NMR: The  $^1\text{H}$  NMR spectra of the two products were indistinguishable from each other and corresponded to that of the input material.

*UV and CD:*

*First-eluted enantiomer:*

UV:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 198 and 231 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  58000 and 20400);

CD:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 193, 203 and 231 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  -38.1, +11.4, and +7.5).

Anisotropy factor:  $g_{231} = +3.7 \times 10^{-4}$ .

*Second-eluted enantiomer:*

UV:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 198 and 231 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  58400 and 20800);

CD:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 193, 204 and 231 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  +35.0, -11.3, and -6.9).

Anisotropy factor:  $g_{231} = -3.3 \times 10^{-4}$ .

#### 7.4.7 *Variation of Reaction Conditions in an Attempt to Improve the Yield of 1-Methyl-2,5-Diphenylsilacyclopentane (6)*



Experiments to improve the yield of **6** and to increase the scale of reaction were discussed earlier and the results summarised in Table 3.3. More comprehensive experimental data are shown in Table 7.7; the numbered experiments relate to those listed in Table 3.3. Experiment number one was described under section 7.4.5. Other experiments listed in the table were carried out under similar conditions, with the exceptions noted in the table. Most reactions were not worked up, the yield normally being estimated following NMR spectroscopy of a sample from the reaction mixture. The yield was determined from the ratio of product SiCH<sub>3</sub> integral to total SiCH<sub>3</sub> integral. The typical sample preparation procedure for NMR spectroscopy was: 200 µl of reaction mixture was sampled using a Gilson pipette, transferred to 500µl of CDCl<sub>3</sub> and the precipitated metal chloride separated by centrifuge before removing the supernatant for NMR analysis. All pipette tips and glassware, including NMR tubes, were stored in an oven (*ca.* 70°C) prior to use. CDCl<sub>3</sub> was stored over 4A molecular sieve.

Expt	Equivalents of reagents		Scale	Metal	Temp <sup>1</sup>	Conditions	Yield <sup>2</sup>
	Styrene (vol.) <sup>3</sup>	CH <sub>3</sub> SiHCl <sub>2</sub> (vol.) <sup>3</sup>	mol vol <sub>T</sub> <sup>4</sup>	Metal form <sup>5</sup>	Total vol THF		
1	1 50ml	1 50ml	0.144 100ml	Li shot	0°C	Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 40 min. Reaction mixture stirred for 16 hours at 18°C	8.8%
2	1 50ml	1.2 50ml	0.144 100ml	Li shot	0°C	Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 30 min	6.9%
3	1 50ml	2 50ml	0.144 100ml	Li shot	<10°C	Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 5 min. Further Li added after 3 h.	8.3%
4	1 25ml	1 25ml	0.144 150ml	Li shot	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 80 min. Excess styrene found in final reaction mixture	15%
5	1.4 110ml	1 50ml	0.1 160ml	Li shot	<10°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 5 hours.	13%

Expt	Equivalents of reagents		Scale	Metal	Temp <sup>1</sup>	Conditions	Yield <sup>2</sup>
	Styrene (vol.) <sup>3</sup>	CH <sub>3</sub> SiHCl <sub>2</sub> (vol.) <sup>3</sup>	mol vol <sub>T</sub> <sup>4</sup>	Metal form <sup>5</sup>	Total vol THF		
6	1 40ml	1 40ml	0.05 80ml	Li shot	<10°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 50 min. Both styrene and CH <sub>3</sub> SiHCl <sub>2</sub> remained, stirring continued at 18°C for 20 h.	6%
7	1 20ml	1 20ml	0.05 40ml	Li shot	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 90 min	6%
8	1 40ml	1 40ml	0.05 80ml	Li shot	<-60°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 2 hours	6%
9	1 40ml 1	1 40ml	0.05 80ml	Li shot	<-60°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 1 hour. Fresh lithium used (lower sodium content)	6%
10	1 40ml	1 40ml	0.05 80ml	Li pwrdr	<10°C	CH <sub>3</sub> SiHCl <sub>2</sub> added to styrene over 1 hour. Fresh lithium with high sodium content used	5%
11	1 40ml	1 40ml	0.05	K wire	<15°C	Styrene solution placed in flask with freshly-pressed potassium wire (→ red colour on surface). CH <sub>3</sub> SiHCl <sub>2</sub> added over 1 hour. Higher mass of metal hindered stirring.	~0%
12	1 20ml	1 20ml	0.05 40ml	K	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 90 min.	~2%
13	1 20ml	1 20ml	0.05 80ml	Na wire	<10°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 60 min to freshly pressed sodium wire. Refer to comments following this table.	15%
14	1 20ml	1 20ml	0.05 80ml	Na wire	<-60°C	Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 60 min. After addition, stirred at 8°C for 16hr.	8%
15	1 20ml	1 20ml	0.05 80ml	Na wire	<-60°C		<3%

Expt	Equivalents of reagents		Scale	Metal	Temp <sup>1</sup>	Conditions	Yield <sup>2</sup>
	Styrene (vol.) <sup>3</sup>	CH <sub>3</sub> SiHCl <sub>2</sub> (vol.) <sup>3</sup>	mol vol <sub>T</sub> <sup>4</sup>	Metal form <sup>5</sup>	Total vol THF		
16	1 0ml	1 80ml	0.05 80ml	Na spheres	<-60°C	THF better dried (over LiAlH <sub>4</sub> ). Styrene added neat to CH <sub>3</sub> SiHCl <sub>2</sub> and Na (spheres) over 30 min. Sampled at 40 min and 3.5 h. No red colouration, no products/byprods. 7% product after 48h. Ultrasonication accelerated reaction: mixture → red and yield =10%.	10%
17	1 0ml	1 80ml	0.05 80ml	Na spheres	20°C then reflux	THF ex-LiAlH <sub>4</sub> . Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 30 min with no temp control. 4% product present. After 45 min, T rose to 35°C. After further 40 min, mixture refluxed. 5% product present. Reaction mixture red after stirring overnight at 18°C	8%
18	1 0ml	1 80ml	0.05 80ml	Na spheres	<10°C	'Anhydrous' THF ex-Aldrich. Styrene added to CH <sub>3</sub> SiHCl <sub>2</sub> over 10 min	7%
19	1 0ml	1 0ml	0.05 80ml	Na spheres	<-70°C	'Anhydrous' THF ex-Aldrich. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 120 min.	13%
20	1 0ml	1 0ml	0.25 80ml	Na spheres 1eq.	<-60°C	'Anhydrous' THF ex-Aldrich. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 70 min.	8%
21	1 0ml	1 0ml	1.0 500ml	Na spheres 1.0eq.	<-50°C	'Anhydrous' THF ex-Aldrich. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 45 min. Overhead mechanical stirrer used. After 48h, most residual sodium was fused together in one lump 0.6equiv. sodium remained.	7% 0% <sup>6</sup>
22	1 0ml	1 0ml	1.0 500ml	Na 0.5cm chunks 0.6 eq	<-25°C	As expt 21. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 3 h.. After this, temperature uncontrolled; rose to 50°C	8%

Expt	Equivalents of reagents		Scale	Metal	Temp <sup>1</sup>	Conditions	Yield <sup>2</sup>
	Styrene (vol.) <sup>3</sup>	CH <sub>3</sub> SiHCl <sub>2</sub> (vol.) <sup>3</sup>	mol vol <sub>T</sub> <sup>4</sup>	Metal form <sup>5</sup>	Total vol THF		
23	1  0ml	1  0ml	1.0  500ml	Na 0.5cm chunks 0.7 eq	<-50°C	As expt 21. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 70 min. Different CH <sub>3</sub> SiHCl <sub>2</sub> batch (ex-Hüls-Petrarch Systems) used. After addition, temperature controlled 0-20°C for 8h. Worked up by evaporating THF, dissolving in CH <sub>2</sub> Cl <sub>2</sub> and extracting 6 from polymer with methanol. This gave 10% yield of product containing only small amounts of polymer and styrene.	8%
24	1  0ml	1  0ml	1.0  500ml	Na 0.5cm chunks 0.66eq	0-5°C	'Anhydrous' THF ex-Fluka. Styrene and CH <sub>3</sub> SiHCl <sub>2</sub> added together over 2.5 hours. After 44h at 18°C, some styrene and CH <sub>3</sub> SiHCl <sub>2</sub> remained. More sodium (0.13eq) added and left stirring at 0-5°C for further 60h.	8%

Table 7.7 Summary of experiments to improve the yield of 6.

- Notes:
1. Temperature controlled during addition of reagent
  2. Yield of isolated *crude* product or, in cases where product not worked up, yield based on NMR spectrum of crude product (from ratio of integrals of product SiCH<sub>3</sub> signals to total SiCH<sub>3</sub> signals)
  3. Volume of THF used with reagent (noted as equal volumes where styrene and CH<sub>3</sub>SiHCl<sub>2</sub> added together)
  4. Total volume of THF used.
  5. Physical form of the metal.
  6. After CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> extractions. See text below.

Experiment 13 was fairly typical of the later results. After *ca.* 24 hours, a red suspension remained which persisted for a number of days if the mixture was left untreated. Sampling of the mixture invariably led to a reaction in which the mixture turned whitish in colour, accompanied by some effervescence. This reaction on exposure to air was believed to be due to hydrolysis. Attempts to improve the handling qualities of the thick suspension by dilution with CH<sub>2</sub>Cl<sub>2</sub> increased the rate of reaction, presumably due to the presence of

water in the solvent. Adding water to the slurry resulted in vigorous effervescence. In some cases residual metal was present, but was difficult to observe owing to the nature of the slurry.

Note that the colour of the reaction mixture after stirring overnight was normally blue/grey. The appearance of the red colouration in some reactions did not correlate with the success (or failure) of the reaction. NMR analysis of reaction mixtures at any stage of any of the reactions never provided evidence for the formation of product with a yield greater than 15%.

The alkali metal was originally used in slight excess, but was usually evident at the end of the reaction, consistent with there being a significant amount of polymerisation of styrene following initiation. In experiment 21, one lump of sodium was removed, but it was difficult to remove all the residual sodium. During the work-up with methanol/dichloromethane there was considerable effervescence, which may have been due to the reactive by-products, or to the remaining flecks of sodium. The extracts contained approximately 0% product. In experiment 22, using 0.6 equivalents of sodium, there appeared to be no sodium remaining after 44 hours stirring at 18°C. There was a small amount of styrene and dichloromethylsilane remaining, according to the NMR. Methanol was added to precipitate polymer, causing brief effervescence due to reaction with residual dichloromethylsilane. A total of 1.4 litres of methanol was added to the stirred mixture. In this case, no chlorinated solvent was added and the methanolic extracts were evaporated to give 80g (32% th.) crude product, which was distilled at 35mm Hg to yield four fractions. The isomer ratio of these fractions (from NMR integrals) is shown in Table 7.8.

Fraction	bp / °C	Yield / g	SiCH <sub>3</sub> isomer integral ratio from NMR data		
			$\delta_{\text{H}}=0.4$	$\delta_{\text{H}}=0.0$	$\delta_{\text{H}}=-0.5$
			(9)	(7)	(8)
1	126-132	6.8	19.1	63.8	17.0
2	132-134	6.0	19.7	64.9	15.3
3	134-138	4.1	19.9	67.1	13.0
4	138-190	2.5	20.3	70.6	9.1

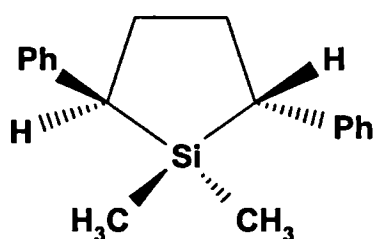
Table 7.8 Yields and isomer ratios of fractions obtained from distillation of crude 6

Samples of fractions 1 and 3 were placed in sealed vials at  $-20^{\circ}\text{C}$ . After 24h, very small feathery crystals were obtained from fraction 1. After 5 weeks approximately half of this fraction was liquid and half solid. However, NMR showed these to be indistinguishable. Fraction 5 became a thick gum after 5 weeks at  $-20^{\circ}\text{C}$ .

The lower layer that remained following the methanolic work-up of experiment 22 was evaporated and analysed by NMR (Figure 3.7). Main features were: some product 6 present (2.5% based on SiCH<sub>3</sub> integral ratios), otherwise broad bands, similar to those of polystyrene, the NMR of which was run for comparison.

<sup>13</sup>C spectrum of lower layer residues: Broad bands,  $\delta_{\text{C}}$ : -9, 27 to 45, 123 to 129, 142 to 145.

In the work-up of experiment 24, the usual grey gelatinous reaction mixture was filtered through a Buchner funnel (no filter paper) to remove sodium, then the filtrate was thinned with THF (200ml) and filtered through filter paper, then extracted as in expt. 23. The crude product (33g) was combined with that from expt. 23 and distilled at 0.2mm Hg to produce 20.7g pure 6 (major fraction bp 131-134°C at 0.2mm Hg).



THF was freshly distilled prior to use as solvent and for washing the lithium shot. The lithium (3.6 g, 0.52 mol) was placed with THF (100 ml) in a 250 ml flask with a magnetic stirrer under a nitrogen atmosphere. A mixture of dichlorodimethylsilane (17.5 ml, 0.14 mol) and styrene (33 ml, 0.29 mol) was placed in a pressure-equalising dropping funnel with THF (50 ml). The flask was chilled to 0°C and the temperature maintained below 15°C as the chlorosilane / styrene mixture was added over 2 h. The reaction was sampled for NMR analysis after 1.3 h and 2 h, treated in the usual way for reaction mixture monitoring (*i.e.* 200  $\mu$ l added to dry  $\text{CDCl}_3$  (500  $\mu$ l) and any precipitated salt separated by centrifuge). The reaction was allowed to continue at 15-20°C overnight, after which time the mixture was analysed by GC/MS.

NMR analysis at 1.3 h: Product isomers apparent with approximate  $\delta_{\text{H}}$ : -0.5 (s), 0.0 (s), 0.5 (s). Also singlets at 0.3, 0.35. No singlet at 0.9 ppm (*i.e.* no remaining  $((\text{CH}_3)_2\text{SiCl}_2)$ ).

NMR analysis at 2 h: similar to above.

Initial GC/MS analysis of final product mixture: two product isomers,  $t_{\text{R}}$ /s: 581 and 586, in the ratio 0.9 : 1.0.

The reaction mixture was filtered to remove excess lithium and lithium chloride. On evaporation of THF, further precipitation of salt (soluble in  $\text{H}_2\text{O}$ ) occurred. The final supernatant was a pale yellow mobile liquid, 44 g. The crude product was purified on a column of Sorbsil C60-A40/60 which was prepared in hexane and eluted with  $\text{CH}_2\text{Cl}_2$  / hexane (1 : 2 v/v). Product was detected after *ca.* 200 ml of eluent had been passed. Fractions were assessed by GC/MS and pooled accordingly. Evaporated fractions totalled 12.66 g, 33%. GC/MS resolved the *Z*- and *E*- isomers, and showed that the flash chromatography hardly resolved them.

GC/MS (method A) analysis of best fraction: 3 GC product peaks:

$t_R$  / s: 416 (17% total peak area) identified as 1,4-diphenylbutane; EIMS  $m/z$ : 210 ( $M^+$ , 23%), 104 (10), 93 (10), 92 (53), 91 (100), 78 (8), 77 (9), 65 (30).

$t_R$  /s: 577 and 583, (with peak area ratio 1.0 : 1.0), 2 components with indistinguishable mass spectra: (EIMS  $m/z$ : 266 (100), 162 (34), 149 (32), 148 (30), 147 (68), 121 (46), 117 (66), 91 (30). (Only scanned to 60 amu.)

$^1H$  NMR of an earlier fraction was complicated by impurities but contained the products with  $\delta_H$ : -0.66 and 0.28 (3 H, 2 s,  $SiCH_3$ ), -0.16 (3 H, 2 s,  $SiCH_3$  *E*-), 2.0-2.7 (6 H, m, 2  $\times$  CH, 2  $\times$   $CH_2$ ), 7.2-7.4 (10 H, m, 2  $\times$  Ph). *cpw* lit.<sup>322</sup> ( $CCl_4$ ): -0.64 and 0.29 (3 H, 2 s,  $SiCH_3$  *Z*-), -0.14 (3 H, 2 s,  $SiCH_3$  *E*-), 2.3 (6 H, m, 2  $\times$  CH, 2  $\times$   $CH_2$ ), 7.1 (10 H, m, 2  $\times$  Ph).

#### 7.4.9 *1-Chloro-1-methyl-2,5-diphenylsilacyclopentane (10)*

Silacyclopentane (0.5 g, as the mixture of diastereoisomers, 7, 8 and 9) was dissolved in  $CCl_4$  (10 ml) and a slow stream of  $Cl_2$  bubbled through the stirred mixture at 0-10°C  $^1H$  NMR showed collapse of the  $SiCH_3$  doublet after <2h. No further change was observed after 3h. Evaporation of the solvent gave a yellow oil (0.65g, 104%).

EIMS (VG20-250, direct insertion):  $m/z$  288 ( $[M+2]^+$ , 20%), 286 ( $M^+$ , 49%), 118 (32), 117 (100), 115 (27), 105 (30), 104 (54), 103, (22), 91 (49), 78 (21).

$^1H$  NMR  $\delta_H$ : -0.17, 0.29, and 0.66, in ratio 20:74:6 (3 H, 3 s,  $SiCH_3$ , 3 diasts). Refer to analysis of 10 prepared from isomerically purified 7 for full NMR data.

In one chlorination reaction, a solution that was only partially chlorinated was left for 16 hours. The NMR was checked before the addition of chlorine, and before and after this period, and then again after a final addition of chlorine. The initial ratio of silane isomers was 20:66:15 (isomers 9:7:8). After initial chlorination the ratio was 8:19:3. After leaving the solution for 16 h the ratio of 9:7 was 8:2. No silane remained after the final chlorination. After initial chlorination, the ratio of the chlorosilane (10) isomers was 10:49:11 (isomers *E-meso*:-: *racemate* : *Z-meso*-). Data was incomplete and not available for the chlorosilane (10) isomer concentrations after leaving the solution for 16 h. After the final chlorination the chlorosilane isomer ratio was 8:68:24.



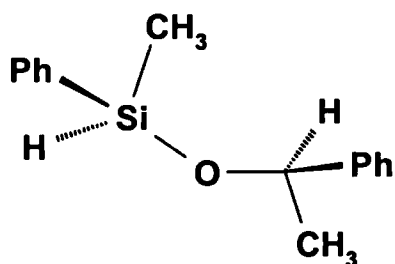
The product was distilled at 0.001 mm Hg to yield two fractions, both straw yellow, (bp 125°C, 115 mg), and RJC 5/3 (bp 130-200°C, 30 mg) (23% th.). A dark brown residue remained in the distillation flask. Other preparations were more successful: *e.g.* from **6** (2.63 g) distilled fractions of high purity **10** were prepared in 86% yield by slow addition of Cl<sub>2</sub> and frequent monitoring by NMR (the chlorination was carried out in the distillation apparatus, set up with a Teflon sampling / purging line). After the chlorination was complete, dissolved Cl<sub>2</sub> and HCl were removed by purging the solution with N<sub>2</sub> prior to applying the vacuum and distillation.

<sup>1</sup>H NMR of sample of **10** prepared from isomerically purified **7** (CHCl<sub>3</sub> ref.): δ<sub>H</sub> 0.31 (3 H, s, CH<sub>3</sub>), 1.92 (1 H, dddd *J* 13, 13, 13, and 4, CH<sub>2</sub>), 2.12 (1 H, dddd *J* 13, 13, 13, and 4, CH<sub>2</sub>), 2.41 (1 H, m, CH<sub>2</sub>), 2.49-2.53 (2 H, m, CH+CH<sub>2</sub>), 2.86 (1 H, dd, *J* 8 and 13, CH), 7.17-7.20 (3 H, m, Ph), 7.31-7.34 (2 H, m, Ph);

<sup>1</sup>H-<sup>1</sup>H COSY NMR: Coupling correlations were observed between the protons at δ<sub>H</sub>/ppm: 1.92 and 2.12, 2.5, and 2.86; 2.12 and 2.41, 2.5; 2.4 and 2.5; 2.5 and 2.86.

<sup>13</sup>C NMR: δ<sub>C</sub>: -0.3 (CH<sub>3</sub>), 31.3 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub> weak, impurity?), 37.8, (CH, inc. impurity?), 39.0 (CH), 39.8 (CH), 125.4, 125.5, 126.9, 127.2, 127.6, 128.8, 128.9, 129.1 (Ar, C2-C5), 141.3, 142.2, (ipso-Ar), 142.6 (weak, impurity, ipso-Ar?).

#### 7.4.10 *Methylphenylsilyl 1-phenethyl ether (1a)*



Racemic chlorosilane **1** (45 μl, 0.30 mmol) in deuteriochloroform (1.0 ml) was added to (±)-1-phenylethanol (37 μl, 0.30 mmol) and was allowed to react at 25°C for 20 min after which time the NMR spectrum (i) was recorded. Pyridine (120 μl, 1.5

mmol) was added and the mixture allowed to react at 25°C for 5 min before repeating the NMR spectrum (ii). The reaction mixture was washed with 2 × 200 μl D<sub>2</sub>O, dried over MgSO<sub>4</sub> and analysed by NMR (iii) and GC/MS.

<sup>1</sup>H NMR of reaction mixture showed: i) no product formed. ii) product formed: δ<sub>H</sub>: 0.38 and 0.41 (3H, 2d<sub>J</sub>3, SiCH<sub>3</sub> of 2 diasts), 1.43 and 1.47 (3H, 2d<sub>J</sub>6, CCH<sub>3</sub> of 2 diasts), 4.90

(1H, mJ6, CH of 2 diasts), 5.01 and 5.08 (1H, mJ3, SiH of 2 diasts), 7.22-7.61 (10H, m, Ar of 2 diasts). iii) product decomposed; new aliphatic signals for 3 compounds: a) 0.42 (3H, d J3, SiCH<sub>3</sub>), 5.20 (1H, q J3, SiH); b) 0.47 (3H, d J3, SiCH<sub>3</sub>), 5.16 (1H, q J3, SiH); c) 1.49 (3H, dJ6, CCH<sub>3</sub>), 4.89 (1H, qJ6, CH).

GC/MS: (Run on reaction mixture after D<sub>2</sub>O) 2 major peaks:

*t<sub>R</sub>*: 356 s (42% total peak area, *t<sub>R</sub>* and EIMS corresponding to 1-phenylethanol);

*t<sub>R</sub>*: 507 s (52% total peak area, EIMS m/z: 258 ((PhCH<sub>3</sub>SiH)<sub>2</sub>O, M<sup>+</sup>, 10%), 257 (12), 243 (9), 181 (19), 180 (38), 179 (75), 166 (27), 165 (100), 121 (30), 105 (18), 78 (15), 51 (25), 43 (36)).

*Experiment repeated on larger scale*

(±)-1-phenylethanol (370 µl, 3.0 mmol) was added to racemic chlorosilane **1** (450 µl, 3.0 mmol) in deuteriochloroform (1.0 ml) in an NMR tube. On adding pyridine (480 µl, 6.0 mmol) there was an exothermic reaction and a white precipitate was immediately formed. After 10 min the supernatant was decanted and analysed by NMR and GC/MS.

<sup>1</sup>H NMR: δ<sub>H</sub>: 0.37 and 0.40 (3H, dJ3, SiCH<sub>3</sub> of 2 diasts), 1.42 and 1.46 (3H, dJ6, CCH<sub>3</sub> of 2 diasts), 4.88 (1H, mJ6, CH of 2 diasts), 5.01 and 5.09 (1H, mJ3, SiH of 2 diasts), 7.22-7.61 (10H, m, Ar of 2 diasts). 7.3-8.6 (*ca.* 0.7 mole × 5H, m, pyridine).

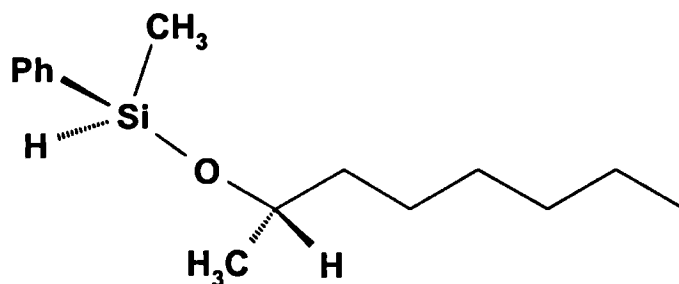
GC/MS: 4 GC peaks:

*t<sub>R</sub>* 359 s: (11% total peak area, *t<sub>R</sub>* and EIMS corresponding to 1-phenylethanol);

*t<sub>R</sub>* 512 s: (11% total peak area, EIMS m/z: 258 ((PhCH<sub>3</sub>SiH)<sub>2</sub>O, M<sup>+</sup>, 6%), 257 (3), 243 (7), 180 (41), 179 (79), 165 (100), 121 (28), 105 (15), 78 (22), 51 (21), 43 (27)).

*t<sub>R</sub>* 516 and 519 s: (78% total peak area, EIMS: indistinguishable spectra, m/z: 241 ([M-1]<sup>+</sup>, 7%), 227 ([M-15]<sup>+</sup>, 8%), 137 ([M-105]<sup>+</sup>, 100%), 121 (38), 105 (59), 77 (32), 51 (23), 45 (37), 43 (29). The two diastereoisomers of **1a** were separated with separation factor, α = 1.006 and peak resolution, *R<sub>s</sub>* = 1.30.

#### 7.4.11 *Methylphenylsilyl 2-octyl ether (1b)*



Racemic chloromethylphenylsilane (**1**) (45  $\mu$ l, 0.30 mmol) in deuteriochloroform (1.0 ml) was added to (*S*)-(+)-2-octanol (47.5  $\mu$ l, 0.30 mmol) and pyridine (120  $\mu$ l, 1.5 mmol) and allowed to react at 20°C for 20 min before recording the GC/MS and the NMR spectrum.

$^1\text{H}$  NMR of reaction mixture showed product formed:  $\delta_{\text{H}}$ : 0.44 (3H, 2d,  $\text{SiCH}_3$  of 2 diasts), 0.86 (3H, m,  $\text{CH}_3\text{CH}_2$  of 2 diasts), 1.13 and 1.17 (3H, 2d,  $\text{CH}_3\text{CO}$  of 2 diasts), 1.20-1.50 (10H, m, aliphatic of 2 diasts), 3.84 (1H, m, CHO of 2 diasts), 5.07 (1H, m, SiH of 2 diasts), 7.34-7.63 (5H, m, aromatic of 2 diasts)

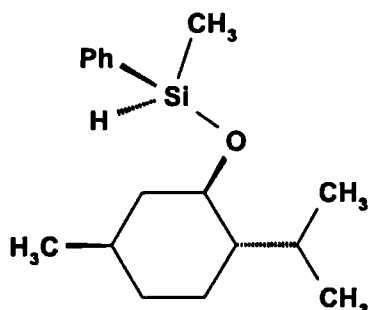
GC/MS (product mixture, GC method B): 4 peaks;

$t_{\text{R}}$ : 324 s (18% of total peak area,  $t_{\text{R}}$  and EIMS corresponding to 2-octanol);

$t_{\text{R}}$ : 499 s and 502 s (32% and 35% total peak area, EIMS: indistinguishable spectra,  $m/z$ : 249 ( $[\text{M}-1]^+$ , 4%), 172 (9), 165 (63), 147 (49), 138 (15), 137 ( $[\text{PhSiCH}_3\text{OH}]^+$ , 100%), 123 (30), 121 (72), 105 (18), 61 (61), 55 (16), 45 (44). The two diastereoisomers of **1b** were separated with separation factor,  $\alpha = 1.006$  and peak resolution,  $R_s = 1.41$ .

$t_{\text{R}}$ : 514 s (15% total peak area, EIMS:  $m/z$ : 257 ( $(\text{PhSiHCH}_3)_2\text{O}$ ,  $[\text{M}-1]^+$ , 3%), 243 (6), 195 (7), 181 (14), 180 (32), 179 (78), 166 (20), 165 (100), 121 (31), 105 (17), 78 (27), 51 (23)).

#### 7.4.12 *Methylphenylsilyl menthyl ether (1c)*



Racemic chloromethylphenylsilane (**1**) (45  $\mu$ l, 0.30 mmol) in deuteriochloroform (1.0 ml) was added to menthol (42.6 mg, 0.30 mmol) and pyridine (120  $\mu$ l, 1.5 mmol) and allowed to react at 25°C for 30 min before

recording the NMR spectrum. GC/MS analysis was run after 24 h.

$^1\text{H}$  NMR of product (not isolated):  $\delta_{\text{H}}$ : 0.44 and 0.45 (3H, 2d,  $\text{SiCH}_3$  of 2 diasts), 0.60, 0.75, 0.84, 0.87, 0.88, 0.89 (9H, 6d, menthyl  $\text{CH}_3$  of 2 diasts), 0.8-2.3 (9H, m, aliphatic of 2 diasts), 3.47 and 3.50 (1H, 2dt, CHO of 2 diasts), 5.10-5.11 (1H, m, SiH of 2 diasts), 7.35-7.63 (5H, m, aromatics of 2 diasts).

GC/MS (product mixture, GC method B): 3 GC peaks:

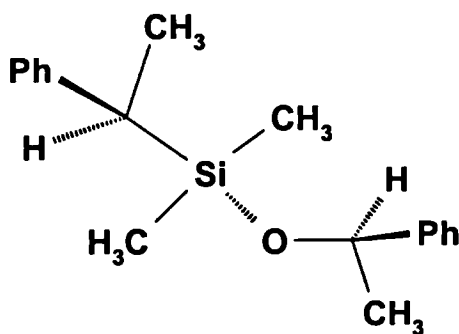
$t_{\text{R}}$ : 398 s (11% total peak area, EIMS corresponding to menthol); 95 (46), 82 (30), 81 (94), 71 (64), 67 (60), 57 (25), 55 (47), 43 (56), 41 (100), 39 (59).

(For comparison, menthol previously analysed under slightly different conditions: GC method C with threshold  $m/z$  40:  $t_{\text{R}}$  370 s (EIMS  $m/z$ : 95 (60), 82 (24), 81 (93), 71 (57), 69 (20), 67 (50), 57 (27), 55 (46), 43 (56), 41 (100)).

$t_{\text{R}}$ : 507 s (6% total peak area, EIMS  $m/z$ : 258 ( $[(\text{PhSiCH}_3\text{H})_2\text{O}]^+$ , 4%), 243 (9), 181 (20), 180 (31), 179 (81), 166 (26), 165 (100), 121 (28), 78 (28), 43 (28));

$t_{\text{R}}$ : 534 s (83% total peak area, EIMS  $m/z$ : 275 ( $[\text{M}-1]^+$ , 5%), 198 (38), 191 (55), 137 ( $[\text{PhSiCH}_3\text{OH}]^+$  93%), 121 (50), 113 (52), 95 (47), 81 (57), 43 (76), 41 (100), 39 (44)).

#### 7.4.13 Dimethyl-1-phenethylsilyl 1-phenethyl ether (3a)



##### a) attempted reaction in absence of base

( $\pm$ )-1-Phenylethanol (37  $\mu\text{l}$ , 0.30 mmol) was placed in an NMR tube with 0.6 ml  $\text{CDCl}_3$  and chlorosilane 3 (50  $\mu\text{l}$ , ca. 0.30 mmol) was added. The mixture was allowed to react at  $25^\circ\text{C}$  and was analysed by NMR and GC/MS after 16 h. and 6 days.

$^1\text{H}$  NMR ( $t=16$  h): no change.

$^1\text{H}$  NMR ( $t=6\text{d}$ ): complex mixture, largest new signals,  $\delta_{\text{H}}$ : -0.08 (m,  $\text{SiCH}_3$ ), 0.07 (d,  $\text{SiCH}_3$ ), 1.83 (d,  $\text{CH}_3$ ), 4.85 (q,  $\text{CHCH}_3$ ).

Reduced signals:  $\delta_{\text{H}}$ : 0.31, 0.33 (6H, 2s,  $\text{SiCH}_3$ ), 1.46 ((3H, d,  $\text{CH}_3\text{CHSi}$ ) + (3H, d,  $\text{CH}_3\text{CHOH}$ )), 2.42 (1H, q,  $\text{CHSi}$ ), 4.85 (1H, q,  $\text{CHOH}$ ).

GC/MS ( $t=16\text{ h}$ ): little change.

GC/MS ( $t=6\text{d}$ ): 7 GC peaks:

$t_{\text{R}}$  356 s (38% total peak area,  $t_{\text{R}}$  and EIMS corresponding to 1-phenylethanol);

$t_{\text{R}}$  421 s (22% total peak area, 2 near-coincident compounds: EIMS  $m/z$ : 200 ( $\text{PhCHCH}_3\text{Si}(\text{CH}_3)_2\text{Cl}$ ,  $[\text{M}+2]^+$ , 10%), 198  $[\text{M}]^+$ , (24), 105 (62), 104 (95), 95 (37), 93  $[(\text{CH}_3)_2\text{SiOH}]^+$ , (100), 77 (28), 75 (42%, probably coeluted silanol), 65 (27), 63 (36), 51 (23) and 180 ( $\text{PhCHCH}_3\text{Si}(\text{CH}_3)_2\text{OH}$ ,  $[\text{M}]^+$ , 4%), 137 (3), 105 (4), 103 (3), 77 (10), 75  $[(\text{CH}_3)_2\text{SiOH}]^+$ , 100%), 47 (13), 45 (16);

$t_{\text{R}}$  504 and 508 s (each 3% total peak area, near-identical EIMS spectra,  $m/z$ : 121( $[\text{PhCHCH}_3\text{O}]^+$ , 11%), 106 (19), 105 (100), 79 (19), 77 (30), 51 (17);

$t_{\text{R}}$  559 s (8 % total peak area, EIMS  $m/z$ : 179, ( $[\text{M}-105]^+$ , 16%), 105 (14), 79 (9), 77 (15), 75 ( $[(\text{CH}_3)_2\text{SiOH}]^+$ , 100), 47 (6);

$t_{\text{R}}$  625 s (24 % total peak area, EIMS  $m/z$ : 327 ( $[\text{M}-15]^+$ , 3%), 237 ( $[\text{M}-105]^+$ , 100%), 209 (27), 193 (18), 133 (63), 105 (29), 79 (20), 77 (18), 73 (21);

*b) reaction in presence of pyridine*

( $\pm$ )-1-phenylethanol (37  $\mu\text{l}$ ., 0.30 mmol) was placed in an NMR tube with 0.7 ml  $\text{CDCl}_3$  and chlorosilane **3** (50  $\mu\text{l}$ , *ca.* 0.30 mmol) was added. After 10 min pyridine (120  $\mu\text{l}$ , 1.5 mmol) was added and the mixture allowed to react at  $25^\circ\text{C}$  and was analysed by NMR and GC/MS after 10 min and 30 min. The NMR was checked after blowing off some of the pyridine with  $\text{N}_2$  at  $20^\circ\text{C}$ , and again after washing the  $\text{CDCl}_3$  solution with  $\text{D}_2\text{O}$  (200  $\mu\text{l}$ ) and drying with  $\text{MgSO}_4$ .

$^1\text{H}$  NMR: ( $t=10$  min): new signals,  $\delta_{\text{H}}$ : -0.05, -0.04, -0.02, 0.02 (6H, 4s,  $\text{SiCH}_3$  of 2 diasts), 1.34-1.43 (6H, m,  $\text{CH}_3\text{CHO}$  &  $\text{CH}_3\text{CHSi}$  of 2 diasts), 2.22, 2.28 (1H, 2q,  $\text{CH}_3\text{CHSi}$  of 2 diasts), 4.77 (1H, m,  $\text{CH}_3\text{CHO}$  of 2 diasts), 7.12-7.41 (10H, m, aromatics of 2 diasts).

$^1\text{H}$  NMR: ( $t=30$  min): no further change.

$^1\text{H}$  NMR: (after evaporation): pyridine : product ratio decreased from 12 : 1.0 to 1.2 : 1.0

$^1\text{H}$  NMR: (after  $\text{D}_2\text{O}$  wash): pyridine : product ratio decreased from 1.2 : 1.0 to 0.0 : 1.0

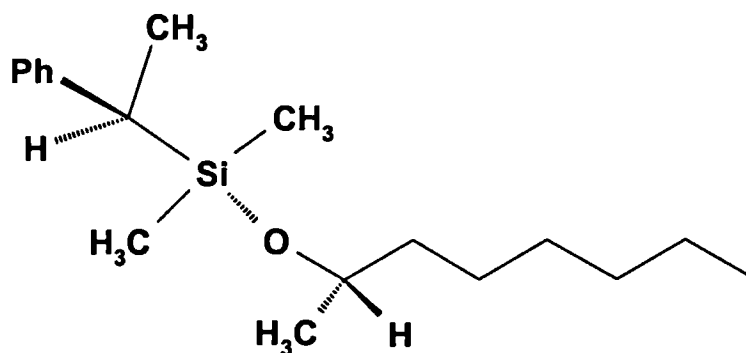
GC/MS: 2 GC peaks:

$t_{\text{R}}$  356 s (12% total peak area,  $t_{\text{R}}$  and EIMS corresponding to 1-phenylethanol);

$t_{\text{R}}$  560 s (88% total peak area, EIMS  $m/z$ : 179 ( $[\text{PhCHCH}_3\text{OSi}(\text{CH}_3)_2]^+$ , 16%), 105 (20), 79 (10), 77 (14), 75 ( $[(\text{CH}_3)_2\text{SiOH}]^+$ , 100), 47 (6).

HPLC (5% DCM / hexane on silica): Above reaction mixture input. 2 peaks eluted at  $t_{\text{R}}$ : 17.9 and 18.7 min, only partially resolved (hold-up time,  $t_{\text{M}} = 8.4$  min; separation factor,  $\alpha = 1.08$  and peak resolution,  $R_s \approx 0.7$ . Fractions of each component were collected. Analysis by GC/MS (method B) gave a single peak in both cases, having the same retention time (560 s) and EIMS as that described above.

#### 7.4.14 Dimethyl-1-phenethylsilyl 2-octyl ether (**3b**)



Chlorosilane **3** (50  $\mu\text{l}$ , *ca.* 0.30 mmol) and dry pyridine (120  $\mu\text{l}$ , 1.5 mmol) were added to (*S*)-(+)-2-octanol (47.5  $\mu\text{l}$ , 0.30 mmol) and the contents well mixed, then allowed to react at 22°C. The NMR spectrum was run after 5 min. After 1.5 h. some pyridine was

evaporated by blowing with N<sub>2</sub>. Excess pyridine and pyridine hydrochloride were extracted with D<sub>2</sub>O (200 µl). The CDCl<sub>3</sub> layer was separated, dried over MgSO<sub>4</sub>, and the NMR spectrum was recorded again. The GC/MS was then recorded.

<sup>1</sup>H NMR (product signals only, some unreacted 2-octanol) δ<sub>H</sub>: 0.00, 0.01, 0.04, 0.04 (6H, 4s, SiCH<sub>3</sub> of 2 diasts), 0.89 (3H, 4t, CCH<sub>3</sub> of 2 diasts), 1.08, 1.09 (3H, 2d, CH<sub>3</sub>CHO of 2 diasts) 1.18-1.42 (10H, m, aliphatics of 2 diasts), 1.39, 1.39 (3H, 2d, CH<sub>3</sub>CHPh of 2 diasts), 2.24 (1H, q, CHPh of 2 diasts), 3.73 (1H, m, CHO of 2 diasts), 7.06-7.46 (5H, m, aromatics of 2 diasts).

The NMR assignments for the CH<sub>3</sub>CH groups in different environments were correlated by <sup>1</sup>H-<sup>1</sup>H COSY data.

<sup>1</sup>H NMR showed that the molar ratio of pyridine : product was reduced from 6.2 : 1.0 to 0.5 : 1.0 by washing the CDCl<sub>3</sub> layer with D<sub>2</sub>O.

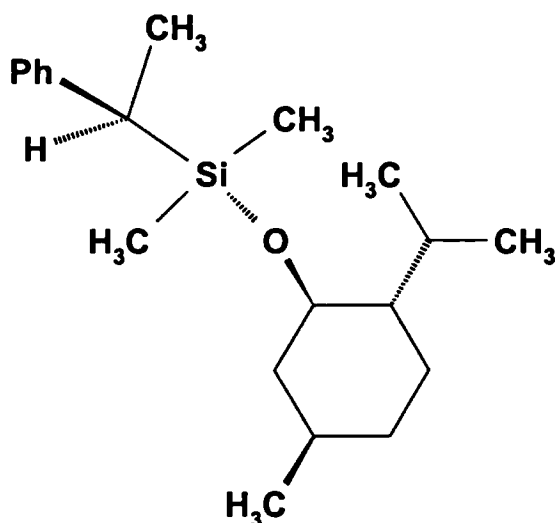
GC/MS (method B): 2 GC peaks:

*t*<sub>R</sub> 323 s (8% total peak area, *t*<sub>R</sub> and EIMS corresponding to 2-octanol);

*t*<sub>R</sub> 542 s (92% total peak area, EIMS m/z: 277 ([M-15], 3%), 187 ([M-105]<sup>+</sup>, 35%), 135 (7), 105 (10), 75 (100), 41 (11)).

HPLC (5% DCM / hexane on silica): Above reaction mixture input. 2 peaks eluted at *t*<sub>R</sub>: 17.0 and 17.5 min, only partially resolved (hold-up volume, *t*<sub>M</sub> = 7.5 min; separation factor, α = 1.05; peak resolution, *R*<sub>s</sub> not quantifiable). Fractions of each component were collected. Analysis by GC/MS (method B) gave a single peak in both cases, having the same retention time (542 s) and EIMS as that described above.

7.4.15 *Dimethyl-1-phenethylsilyl menthyl ether (3c)*



Menthol (44.8 mg, 0.29 mmol) was placed in a 1 ml vial with 0.5 ml  $\text{CDCl}_3$ . Dry pyridine (120  $\mu\text{l}$ , 1.5 mmol) and chlorosilane **3** (50  $\mu\text{l}$ , *ca.* 0.30 mmol) was added and the contents well mixed, then allowed to react at 22°C. Analysis by GC/MS was carried out after 40 min and by NMR and GC/MS after 4 days.

$^1\text{H}$  NMR (product signals only, some unreacted menthol remained)  $\delta_{\text{H}}$ : 0.02, 0.03, 0.05, 0.07 (6H, 4s,  $\text{SiCH}_3$  of 2 diasts), 0.68, 0.69, 0.84-0.89 (9H, 6d, menthyl  $\text{CH}_3$  of 2 diasts), 1.38, 1.40 (3H, 2d,  $\text{CH}_3\text{CHPh}$  of 2 diasts), 1.0-2.3 (9H, m, aliphatics of 2 diasts), 3.38, 3.42 (2H, m,  $\text{CHCH}_3$  and  $\text{CHO}$  of 2 diasts), 7.07-7.39 (5H, m, aromatics of 2 diasts).

GC/MS ( $t=40$  min, method B): 2 GC peaks:

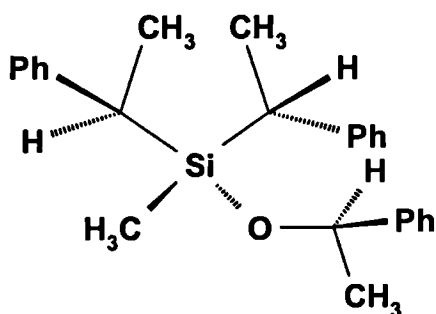
$t_{\text{R}}$  399 s (10% total peak area, EIMS  $m/z$ : 95 (47), 81 (76), 71 (65), 67 (57), 55 (50), 43 (50), 41 (100), 39 (58), corresponding to menthol, ref. Section 7.4.12);

$t_{\text{R}}$  589 s (90% total peak area, EIMS  $m/z$ : 303 ( $[\text{M}-15]$ , 3%), 213 ( $[\text{M}-105]^+$ , 27%), 137 ( $[\text{PhCH}_3\text{SiOH}]^+$ , 20%), 81 (29), 75 (100), 59 (9), 43 (10), 41 (15)).

GC/MS ( $t=4$  d, method B): 2 GC peaks: No further change.

HPLC (5% DCM / hexane on silica): Above reaction mixture input. One major peak eluted at  $t_{\text{R}}$ : 12.6 min. A fraction of this component was collected. Analysis by GC/MS (method B) gave a single peak having the same retention time (589 s) and EIMS as that described above.





Bis(1-phenylethyl)chloromethylsilane (**5**) (87  $\mu$ l, 0.30 mmol) in 0.6 ml  $\text{CDCl}_3$  and pyridine (120  $\mu$ l, 1.5 mmol), was mixed with ( $\pm$ )-1-phenylethanol (37  $\mu$ l., 0.30 mmol), and allowed to react at 20-25°C. The reaction mixture was analysed at intervals by NMR and GC/MS.

$^1\text{H}$  NMR: no change after 5 min, re-recorded after 1 h. <177 (no TMS)>: new signals,  $\delta_{\text{H}}$ : -0.16, -0.14, and -0.01 (3H, 3s,  $\text{SiCH}_3$  of 3 diasts), some alcohol and chlorosilane remained; other changes too small and signals too complex to interpret prior to purification.

GC/MS (method B) recorded after 3 days: 7 GC peaks: (no remaining 1-phenylethanol at  $t_{\text{R}}$  356 s.):

$t_{\text{R}}$  508 and 514 s, (3 and 4% of total peak area), EIMS: 2 components with indistinguishable mass spectra: (EIMS  $m/z$ : 105 ( $[\text{PhCHCH}_3]^+$ , (100%), 104 (29), 103 (13), 79 (26), 78 (9), 77 (23), 51 (14), 39 (9)), corresponding to the dimeric contaminants  $(\text{PhCHCH}_3)_2$  (compare with data in Section 7.4.1).

$t_{\text{R}}$  601, 605 and 607 s, (5, 3 and 4% of total peak area), 3 components with indistinguishable mass spectra: (EIMS  $m/z$ : 270 ( $[\text{M}^+$ , 3%), 165 ( $[\text{PhCHCH}_3\text{SiCH}_3\text{OH}]^+$ , 50%), 137 ( $[\text{PhSiCH}_3\text{OH}]^+$ , 100%), believed to be  $(\text{PhCHCH}_3)_2\text{SiCH}_3\text{OH}$ .

$t_{\text{R}}$  902, 919, and 937 s, (27%, 45% and 9% of total peak area), 3 components with indistinguishable mass spectra: (EIMS  $m/z$ : 269 ( $[(\text{PhCHCH}_3)_2\text{SiCH}_3\text{O}]^+$ , 32%), 251 (33), 165 (28), 137 ( $[\text{PhSiCH}_3\text{OH}]^+$ , 100%), 105 (56), 79 (27), 77 (33), 61 (17), 45 (12).

HPLC (5% DCM / hexane on silica): Above reaction mixture input. 3 peaks eluted at  $t_{\text{R}}$ : 13.8 (medium), 15.4 (large) and 16.4 min (small, not well resolved). Fractions of each component were collected. Analysis by GC/MS (method B) gave a single peak ( $t_{\text{R}}$  902 s) for the first fraction, a single peak ( $t_{\text{R}}$  917 s) for the second, and a major (87% total peak

area) peak (936 s) for the third fraction. In each case, these components had the same EIMS as that described for the three corresponding compounds eluted at 902, 919 and 937 s.

NMR analysis of HPLC fractions:

First fraction:  $\delta_{\text{H}}$ : -0.01 (3H, s, SiCH<sub>3</sub>), 1.14 (3H, d, CH<sub>3</sub>CO), 1.20 (3H, d, CH<sub>3</sub>CSi), 1.30 (3H, d, CH<sub>3</sub>CSi), 2.13 (1H, q, CHSi), 2.23 (1H, q, CHSi), 4.35 (1H, m, CHO), 7.03-7.28 (10H, m, aromatic).

Second fraction:  $\delta_{\text{H}}$ : -0.14 (3H, s, SiCH<sub>3</sub>), 1.20 (3H, d, CH<sub>3</sub>CO), 1.23 (3H, d, CH<sub>3</sub>CSi), 1.45 (3H, d, CH<sub>3</sub>CSi), 2.26 (1H, q, CHSi), 2.28 (1H, q, CHSi), 4.46 (1H, q, CHO), 7.06-7.29 (10H, m, aromatic). Also present was an impurity with  $\delta_{\text{H}}$ : -0.16 (3H, s, SiCH<sub>3</sub>), 1.11 (3H, d, CH<sub>3</sub>CO), 1.30 (3H, d, CH<sub>3</sub>CSi), 1.31 (3H, d, CH<sub>3</sub>CSi), 2.22 (1H, q, CHSi), 2.35 (1H, q, CHSi), 4.41 (1H, q, CHO), 7.06-7.29 (10H, m, aromatic).

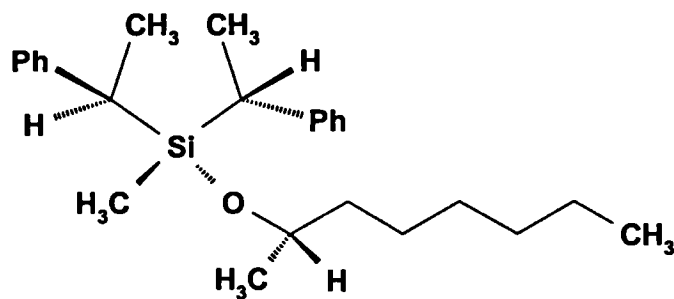
Third fraction:  $\delta_{\text{H}}$ : -0.18 (3H, s, SiCH<sub>3</sub>), 1.24 (3H, d, CH<sub>3</sub>CSi), 1.36 (3H, d, CH<sub>3</sub>CO), 1.42 (3H, d, CH<sub>3</sub>CSi), 2.17 (1H, q, CHSi), 2.24 (1H, q, CHSi), 4.70 (1H, q, CHO), 7.05-7.34 (10H, m, aromatic).

UV and CD:

*First-eluted fraction*: UV:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 225 (not run below 200 nm), ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  14 800); CD:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN) none at *ca.* 230 nm.

*Second-eluted fraction*: UV:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 227 (not run below 193 nm), ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  14 300);

CD:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN) none at *ca.* 230 nm.



Bis(1-phenylethyl)chloromethylsilane (**5**) (62.4 mg, 0.22 mmol) in 0.7 ml  $\text{CDCl}_3$  and pyridine (40  $\mu\text{l}$ , 0.5 mmol), was mixed with (*S*)-(+)-2-octanol (15 mg, 0.12 mmol), and allowed to react for 2 days at 22°C. The NMR and GC/MS were recorded.

$^1\text{H}$  NMR: new signals,  $\delta_{\text{H}}$ : -0.12, -0.04, 0.13, in ratio 1 : 4 : 3 (3H, 3s,  $\text{SiCH}_3$  of 3 diast), some alcohol remained; other changes too small and signals too complex to interpret.

GC/MS (GC method B): 4 major GC peaks:

$t_{\text{R}}$  325 s (9% total peak area,  $t_{\text{R}}$  and EIMS corresponding to 2-octanol);

$t_{\text{R}}$  835 s, 849 s, and 862 s, (29%, 44%, and 9% of total peak area), 3 components with indistinguishable mass spectra: (EIMS  $m/z$ : 279 (6%), 278 (28), 277 ( $[\text{M}-105]^+$ , 100%), 165 (18), 149 (40), 138 (14), 137 (82), 105 (31), 79 (14), 77 (12).

HPLC (5% DCM / hexane on silica): Above reaction mixture input. 3 peaks eluted at  $t_{\text{R}}$ : 10.8 (medium), 12.7 (large) and 13.4 min (small and poorly resolved). Fractions of each component were collected. Analysis by GC/MS (method B) gave a single peak ( $t_{\text{R}}$  820 s) for the first fraction, a single peak ( $t_{\text{R}}$  832 s) for the second, and a major (97% total peak area) peak (843 s) for the third fraction. In each case, these components had the same EIMS as that described for the three corresponding compounds eluted at 835, 849, and 862 s. Retention times of the components in the HPLC fractions were lower than when the product mixture was analysed because the GC column had been shortened since the original analysis.

NMR analysis of HPLC fractions:

First fraction:  $\delta_{\text{H}}$ : 0.12 (3H, s, SiCH<sub>3</sub>), 0.86 (3H, d, CH<sub>3</sub>CO), 0.89 (3H, t, CH<sub>3</sub>CH<sub>2</sub>), 1.25 (3H, d, CH<sub>3</sub>CSi), 1.26 (3H, d, CH<sub>3</sub>CSi), 1.08-1.31 (10H, m, aliphatic), 2.14 (1H, q, CHSi), 2.14 (1H, q, CHSi), 3.46 (1H, m, CHO), 7.07-7.25 (10H, m, aromatic).

Second fraction: (2 isomers)  $\delta_{\text{H}}$ : -0.05 (6H, d, SiCH<sub>3</sub>), 0.85 (3H, d, CH<sub>3</sub>CO), 0.89 (6H, t, CH<sub>3</sub>CH<sub>2</sub>), 0.94 (3H, d, CH<sub>3</sub>CO), 1.28 (3H, d, CH<sub>3</sub>CSi), 1.28 (3H, d, CH<sub>3</sub>CSi), 1.39 (6H, d, CH<sub>3</sub>CSi), 1.08-1.33 (20H, m, aliphatic), 2.23 (2H, m, CHSi), 2.25 (2H, m, CHSi), 3.47 (1H, m, CHO), 3.51 (1H, m, CHO), 7.07-7.25 (20H, m, aromatic).

<sup>13</sup>C spectrum: complex, many signals doubled, but only one SiCH<sub>3</sub> signal (-0.695 ppm).

<sup>29</sup>Si spectrum:  $\delta_{\text{Si}}$ : 7.44, 7.52 (equal area).

Third fraction:  $\delta_{\text{H}}$ : -0.12 (3H, s, SiCH<sub>3</sub>), 0.89 (3H, t, CH<sub>3</sub>CH<sub>2</sub>), 1.09 (3H, d, CH<sub>3</sub>CO), 1.38 (6H, d, CH<sub>3</sub>CSi), 1.23-1.56 (10H, m, aliphatic), 2.19 (2H, m, CHSi), 3.70 (1H, m, CHO), 7.04-7.24 (10H, m, aromatic).

CD and UV data:

*First-eluted fraction:*

UV:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 194, 230, ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  60 500, 15 800);

CD:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 199 and 230 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  -3.6 and -1.1).

Anisotropy factor:  $g_{230} = -7.2 \times 10^{-5}$ .

*Second-eluted fraction:*

UV:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm (not run below 200), 227, ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  14 800);

CD:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 217 and 230 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  -0.3 and +0.5).

Anisotropy factor:  $g_{230} = +3.6 \times 10^{-5}$ .

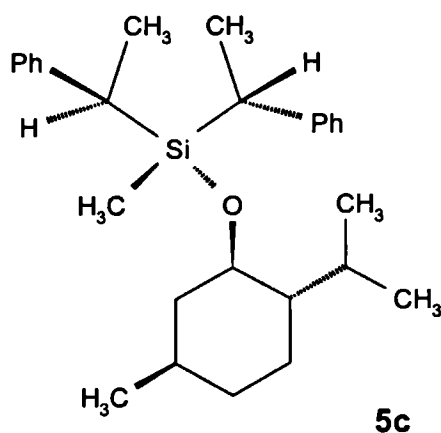
*Third-eluted fraction:*

UV:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 226 (not run below 200 nm);

CD:  $\lambda_{\max}$  (CH<sub>3</sub>CN)/nm 232, +ve (N.B. no quantitative CD or UV data for third fraction of **5b** because minuscule sample prepared; accurate weighing not possible;

anisotropy factor:  $g_{232} = +3.2 \times 10^{-5}$ .

#### 7.4.18 *Bis(1-phenethyl)silyl menthyl ether (5c)*



Bis(1-phenylethyl)chloromethylsilane (**5**) (83 mg, 0.29 mmol) in 0.5 ml CDCl<sub>3</sub> and pyridine (120  $\mu$ l, 1.5 mmol), was mixed with menthol (42 mg, 0.30 mmol), and allowed to react at 25°C. The NMR was recorded at 1.5 h. The GC/MS was only successfully run after 5 w, when the NMR was repeated.

<sup>1</sup>H NMR (t=1.5h.): new signals,  $\delta_{\text{H}}$ : -0.14, -0.06, 0.10 (3H, 3s, SiCH<sub>3</sub>), *ca.* 25% of integral of SiCH<sub>3</sub> in the starting material; other changes too small and signals too complex to interpret.

<sup>1</sup>H NMR (t=5 weeks.): new signals,  $\delta_{\text{H}}$ : -0.16, -0.07, -0.02, -0.01, 0.09, 0.16 (SiCH<sub>3</sub> bands of diastereoisomeric products and by-products), 0.61, 0.62 (3H, 2d, CH<sub>3</sub>), 0.76-2.28 (aliphatics), 3.2-3.3 (1H, m, CHO). Starting materials and by-products present; spectrum too complex to interpret.

GC/MS (GC method B, t=5 weeks.): 8 GC peaks:

$t_{\text{R}}$  397 s (27% total peak area, EIMS m/z: 95 (46), 81 (79), 71 (60), 67 (51), 55 (59), 43 (49), 41 (100), corresponding to menthol, ref. Section 7.4.12);

$t_{\text{R}}$  507 and 513 s (2% and 4% of total peak area), EIMS: 2 components with indistinguishable mass spectra: (EIMS m/z: 106 (8%), 105 ([PhCHCH<sub>3</sub>]<sup>+</sup>, (100%), 104 (26), 103 (13), 79 (21), 78 (8), 77 (23), 51 (11), 39 (7)), corresponding to the dimeric contaminants (PhCHCH<sub>3</sub>)<sub>2</sub> (compare with data in Section 7.4.1).

$t_R$  601 and 604 s (total 15%, EIMS m/z: 270 ( $[M]^+$ , 1%?), 165 ( $[\text{PhCHCH}_3\text{SiCH}_3\text{OH}]^+$ , 53%), 137 ( $[\text{PhCH}_3\text{SiOH}]^+$ , 100%), 105 (17), 79 (16), 77 (22), 61 (19), 45 (27).

$t_R$  975 s, 991 s, and 1014 s (17%, 32%, and 5%), 3 components with indistinguishable mass spectra: (EIMS m/z: 304 (13%), 303 ( $[M-105]^+$ , 66%), 165 (52), 138 (16), 137 (100), 105 (28), 81 (33), 79 (11), 77 (12), 61 (11), 41 (17).

HPLC (5% DCM / hexane on silica): Above reaction mixture input. 2 peaks eluted at  $t_R$ : 12.0 (medium) and 12.7 min (large). Fractions of each component were collected. Analysis by GC/MS (method B) gave a single peak ( $t_R$  969 s) for the first fraction, and a major (85% total peak area) peak ( $t_R$  983 s) for the second fraction. In both cases, these components had the same EIMS as that described for the two corresponding compounds eluted at 975 and 991 s in the GC. The minor diastereoisomeric product (GC  $t_R$  1014s was not isolated by HPLC.

Both fractions were analysed by NMR:

First fraction:  $^1\text{H}$  NMR  $\delta_H$ : 0.15 (3H, s,  $\text{SiCH}_3$ ), 0.60, 0.76 and 0.81 (9H, 3d,  $\text{CH}_3$  of menthyl group), 1.23 and 1.24 (6H, 2d,  $\text{CH}_3\text{CSi}$ ), 0.7-1.5 (8H, m, aliphatics), 2.03 (1H, m, CH), 2.19 (1H, m,  $\text{CHPh}$ ), 2.21 (1H, m,  $\text{CHPh}$ ), 3.22 (1H, m, CHO), 7.09-7.25 (10H, m, aromatics).

Second fraction:  $^1\text{H}$  NMR  $\delta_H$ : -0.03, -0.02 (6H, 2s,  $\text{SiCH}_3$ ), 0.61, 0.64, 0.78, 0.79, 0.84 and 0.87 (18H, 6d,  $\text{CH}_3$  of menthyl group), 1.32 (6H, d,  $2\times\text{CH}_3\text{CSi}$ ), 1.40, (3H, d,  $\text{CH}_3\text{CSi}$ ) 1.41 (3H, d,  $\text{CH}_3\text{CSi}$ ), 0.7-1.6 (16H, m, aliphatics), 2.03 (2H, m, CH), 2.25-2.30 (4H, m,  $\text{CHSi}$ ), 3.28 (2H, m, CHO), 7.01-7.22 (20H, m, aromatics).

*First-eluted fraction:* UV:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 195, 225;

CD:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 199 and 229. Anisotropy factor:  $g_{229} = -7.5 \times 10^{-5}$ .

*Second-eluted fraction:* UV:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ )/nm 195, 227, ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  58 300, 15 000);

CD:  $\lambda_{\max}$  (CH<sub>3</sub>CN)/nm 233 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  -1.5). Anisotropy factor:  $g_{233} = -1.02 \times 10^{-4}$ .

Accurate mass determination: Found: 406.26945 (Within 0.6 ppm of calculated value: C<sub>27</sub>H<sub>38</sub>OSi = 406.26919).

**7.4.19**      *Initial experiments using 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10) to derivatise alcohols.*

Ethanol, 1-butanol, ( $\pm$ )-2-butanol, 3-methyl-2-butanol, 2-heptanol, ( $\pm$ )-1-phenylethanol, (1*R*, 2*S*, 5*R*)-menthol and ( $\pm$ )- $\alpha$ -methyl-2-naphthalenemethanol were derivatised with chlorosilane 10.

*Typical procedure:* The dried alcohol in large excess (0.5 ml, *ca.* 7 mmol) was added under dry N<sub>2</sub> to chlorosilane 10 (2 mg, 7  $\mu\text{mol}$ ) in a vial, which was then sealed and allowed to react at *ca.* 20°C. The reaction was monitored by GC/MS (method A). In all cases three products were formed which were apparently isomeric. There was a by-product, having  $t_R = 655$  s, which was common to all reactions:

*Ethanol derivative (10e)*      GC/MS: 4 GC peaks:

$t_R$  /s: 607, 635 and 648 (with peak area ratio 8 : 75 : 17), 3 components with indistinguishable mass spectra: EIMS  $m/z$ : 297 (24), 296 ( $M^+$ , 100%), 177 (34), 117 (27), 91 (24), 78 (24), 73 (28), 61 (36).

$t_R$  / s: 655 (4% total peak area) EIMS  $m/z$ : 268 ( $M^+$ , 100%), 149 (26), 146 (27), 118 (28), 117 (84), 104 (35), 91 (40), 78 (48), 61 (36).

*1-butanol derivative (10f)*      GC/MS: 4 GC peaks:

$t_R$  / s: 657 (3% total peak area) EIMS  $m/z$ : 268 ( $M^+$ , 100%), 149 (38), 117 (98), 104 (43), 91 (48), 78 (44), 77 (48), 60 (58).

$t_R$  /s: 706, 747 and 774 s, (with peak area ratio 9 : 61 : 30), 3 components with indistinguishable mass spectra: (EIMS m/z: 324 ( $M^+$ , 100%), 163 (47), 149 (26), 105 (25), 104 (30), 91 (27), 78 (34), 61 (61)).

*(±)-2-butanol derivative (10g)* GC/MS: 5 GC peaks:

$t_R$  /s: 654 and 668s, 2 components with indistinguishable mass spectra: EIMS m/z: 268 ( $M^+$ , 100%), 149 (27), 146 (21), 117 (87), 104 (30), 91 (32), 78 (30), 61 (31).

$t_R$  /s: 684, 711 and 727, (with peak area ratio 2 : 88 : 10), 3 components with indistinguishable mass spectra: (EIMS m/z: 324 ( $M^+$ , 100%), 163 (50), 137 (27), 117 (33), 104 (37), 91 (39), 78 (29), 61 (88)).

*3-methyl-2-butanol derivative (10h)*

Note: alcohol not dried. GC/MS printout and data on disk was lost. Recorded data for peaks corresponding to **10h**:

$t_R$  / s: 655 (nnn % total peak area) EIMS recorded as being typical silanol (**10d**).

$t_R$  /s: 3 peaks, major isomer 763s, 3 components with indistinguishable mass spectra: EIMS m/z: 338 ( $M^+$ , 100%), 61 (70), 251 (40).

*2-heptanol derivative (10i)* GC/MS: 3 GC peaks:

$t_R$  /s: 893, 942 and 977, 3 components with indistinguishable mass spectra: EIMS m/z: 366 ( $M^+$ , 100%), 251 (26), 163 (48), 137 (45), 117 (28), 104 (48), 91 (37), 61 (75). Poor mass chromatogram; isomer ratio not determined.

*1-phenylethanol derivative (10a)*

Conditions as above, but alcohol not dried. GC/MS (method A): 4 GC peaks:

$t_R$  / s: 656 (36% total peak area) EIMS m/z: 268 ( $M^+$ , 100%), 149 (31), 117 (99), 104 (30), 91 (32), 78 (36), 77 (24), 61 (32).



$t_R$  /s: 1116, 1191 and 1247, (with peak area ratio 3.6 : 81 : 15), 3 components with indistinguishable mass spectra: (EIMS  $m/z$ : 372 ( $M^+$ , 41%), 163 (100), 137 (34), 117 (33), 105 (79), 79 (31), 77 (34), 61 (33).

The diastereoisomeric products were purified by preparative HPLC on a 250 × 4.6 mm column of 5  $\mu$ m silica, with a mobile phase of dichloromethane/n-hexane (25 : 75 v/v). Three fractions were collected,  $t_R$  /min: 6.3, 7.1 and 7.8. Analysis of these fractions by GC/MS showed that these corresponded to the isomers eluted at 1116, 1191 and 1247 s respectively.

NMR of evaporated fraction containing the major isomer ( $t_R$  = 1191 s in GC/MS):

$\delta_H$ : -0.11 and 0.05 (6 H, 2 s, SiCH<sub>3</sub> of 2 diasts), 1.02 and 1.04 (6 H, 2 d, CH<sub>3</sub>CH of 2 diasts), 4.47 and 4.60 (2 H, 2 q, CHCH<sub>3</sub> of 2 diasts), 7.0-7.2 (30 H, m, Ar of 2 diasts). Aliphatic signals were difficult to distinguish due to small sample size and poor signal to noise ratio.

*(1R, 2S, 5R)-menthol derivative (10c):*

Note: alcohol not dried. Reaction temperature = 70°C. GC/MS: 4 GC peaks:

$t_R$  / s: 658 (16% total peak area) EIMS  $m/z$ : 268 ( $M^+$ , 100%), 149 (29), 117 (85), 104 (34), 91 (31), 78 (31), 61 (28), 60 (22).

$t_R$  /s: 1242, 1337 and 1445, (with peak area ratio 4 : 72 : 24), 3 components with indistinguishable mass spectra: (EIMS  $m/z$ : 406 ( $M^+$ , 100%), 268 (44), 137 (34), 117 (34), 91 (22), 83 (31), 81 (38), 61 (35).

*Investigation of product stereoisomers using an achiral reagent:*

*(±)-1-chloro-1-methyl-2,5-diphenylsilacyclopentane derivative of 3-pentanol (10j):*

A solution of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**), (49.2 mg, 0.17 mmol in 0.25 ml  $\text{CDCl}_3$ ) was added to 3-pentanol (8.5 mg, 0.11 mmol), the vial flushed with dry  $\text{N}_2$ , sealed, and allowed to react at 15-20 °C for 7 days, then at 70°C for 18 h.

GC/MS (GC method C): 3 GC peaks:

$t_R$  /s: 1136, 1159 and 1175s, 3 components (with peak area ratio 3 : 72 : 25) with indistinguishable mass spectra: EIMS  $m/z$ : 339 ( $[\text{M}+1]^+$ , 29%), 338 ( $\text{M}^+$ , 100%), 163 (33), 117 (30), 104 (31), 91 (31), 61 (79), 45 (44), 43 (62), 41 (30).

Small samples of the major product isomers were isolated by normal-phase HPLC on a 250  $\times$  4.6 mm column of 5  $\mu\text{m}$  Apex silica with a mobile phase of dichloromethane / *n*-hexane (6/94 v/v). 2 major product isomers eluted ( $t_R$  /min: 6.2 and 8.8). GC/MS showed that they both had >97% isomeric purity, and that they corresponded to the isomers eluted second and third in the GC (*i.e.* the two major products). These fractions were evaporated with  $\text{N}_2$ , and the  $^1\text{H}$  NMR spectra recorded.

1159 s. isomer,  $\delta_{\text{H}}$ : 0.1 (3 H, s,  $\text{CH}_3\text{-Si}$ ), 0.5 (3 H, t,  $\text{CH}_3\text{-CH}_2$ ), 0.7 (3H, t,  $\text{CH}_3\text{-CH}_2$ ), 1.6 (contains impurity,  $\approx$ 4 H, m,  $2 \times \text{CH}_2$ ), 1.8 - 2.6 ( $\approx$ 6 H, m,  $6 \times$  ring CH), 3.3 (1 H, m,  $\text{CH-}[\text{CH}_2]_2$ ), 7.0 - 7.4 (contains  $\text{CHCl}_3$ ,  $\approx$ 10 H, m, Ar).

1175 s. isomer,  $\delta_{\text{H}}$ : -0.4 (3 H, s,  $\text{CH}_3\text{-Si}$ ), 0.9 (6 H, t,  $2 \times \text{CH}_3\text{-CH}_2$ ), 1.6 (contains impurity,  $\approx$ 4 H, m,  $2 \times \text{CH}_2$ ), 2.2 (4 H, m,  $4 \times$  ring CH), 2.7 (2 H, m,  $2 \times$  ring CH), 3.6 (1 H, m,  $\text{CH-}[\text{CH}_2]_2$ ), 7.0 - 7.4 (contains  $\text{CHCl}_3$ ,  $\approx$ 10 H, m, Ar)

*3-pentanol derivative (10j): derivatisation with purified racemic 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10)*

Chlorosilane **10** was prepared from isomerically-purified **7** (20 mg, 0.079 mmol) in 0.5 ml  $\text{CDCl}_3$  by chlorination in an NMR tube. After purging with dry  $\text{N}_2$  to remove excess  $\text{Cl}_2$ , dried 3-pentanol (5 $\mu\text{l}$ , 4.1mg, 0.046mmol) was added. The reaction mixture was sealed under nitrogen and maintained at 18°C and was monitored by NMR and GC/MS. GC/MS (GC method C): Main single product; when spiked into solution from above experiment

with mixed isomer derivative **10j**, enhanced major peak (corresponding to peak eluted at 1159s above. Slow reaction: estimated 30% after 25 days. Reaction mixture at this time contained residual 3-pentanol and **10** and was not worked up. Sample evaporated: NMR ( $\text{CDCl}_3$ ) of product signals in methyl region:  $\delta_{\text{H}}$ : 0.1 (3 H, s,  $\text{CH}_3\text{-Si}$ ), 0.5 (3H, t,  $\text{CH}_3\text{-CH}_2$ ), 0.7 (3H, t,  $\text{CH}_3\text{-CH}_2$ ).

*Further study of reaction of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane with ( $\pm$ )-2-butanol (**10g**): Reaction with stoichiometric proportions of reagents, using isomerically purified ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane.*

Chlorosilane **10** was prepared from isomerically-purified **7** (16 mg, 0.063 mmol) in 0.5 ml  $\text{CDCl}_3$  by chlorination in an NMR tube. After purging with dry  $\text{N}_2$  to remove excess  $\text{Cl}_2$ , dried (4A molecular sieve) ( $\pm$ )-2-butanol (4.8 $\mu\text{l}$ , 4.7mg, 0.063mmol) was added. The reaction mixture was sealed under nitrogen and maintained at 50°C and was monitored by NMR and GC/MS. The GC/MS in this later work (GC method C) was run with a quite different temperature programme from that used in the initial study of **10g**.

In the absence of base, after 20 h at 50°C, little change in the NMR. GC/MS showed the reagent chlorosilane **10** ( $t_{\text{R}}$ : 1092 s,  $M^{+}=286$ ) was mostly unreacted. After 4 days at 50°C, the NMR showed that the 2-butanol and **10** were still largely unchanged, and the GC/MS confirmed that the chlorosilane **10** was still hardly depleted. Dried pyridine (5.1  $\mu\text{l}$ , 0.063 mmol) was then added and the mixture allowed to react at 20°C for a further 15 hours. After this time, NMR of reaction mixture recorded again, with the following signals in the aliphatic region having increased:

$\delta_{\text{H}}$ : 0.03 and 0.04 (2 $\times$ 3H, 2 $\times$ s,  $\text{SiCH}_3$  of two diasts), 0.55 and 0.69 (2 $\times$ 3H, 2 $\times$ t,  $\text{CH}_3\text{CH}_2$  of two diasts), 0.66 and 0.84 (2 $\times$ 3H, 2 $\times$ d,  $\text{CH}_3\text{CHO}$  of two diasts), 1.15 (2 $\times$ 2H, 2 $\times$ m,  $\text{CH}_2\text{CHO}$  of two diasts), 3.45 (2 $\times$ H, 2 $\times$ m, CHO of two diasts).

*Differences in the rate of reaction of the chiral and the meso-isomers of chlorosilane **10**.*

a) A solution of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**), (98.4 mg, 0.344 mmol in 0.5 ml  $\text{CDCl}_3$ ) was added to (1*R*, 2*S*, 5*R*)-menthol (54.6 mg, 0.35 mmol), the vial flushed with dry  $\text{N}_2$ , sealed, and allowed to react at 15-20 °C for 22 days.

GC/MS (GC method C): 3 GC peaks formed after 24h, with  $t_R$  = 1455, 1516 and 1581s, corresponding to **10c** isomers (on the basis of previous experiments, with base peak of  $m/z$  406). The analysis was repeated after 2, 8 and 22 days; the relative areas of the first, second and third-eluted **10c** peaks are shown in Table 4.14.

b) A solution of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**), (20 mg, 0.07 mmol in 0.1 ml  $\text{CDCl}_3$ ) was added to (1*R*, 2*S*, 5*R*)-menthol (31.2 mg, 0.20 mmol), the vial flushed with dry  $\text{N}_2$ , sealed, and allowed to react at 15-20 °C for 4 days.

GC/MS as in (a) above, analysis repeated after 1, 2.5, 4 hours and 4 days; the relative areas of the first, second and third-eluted **10c** peaks are shown in Table 4.15.

c) A solution of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**), (49.2 mg, 0.17 mmol in 0.25 ml  $\text{CDCl}_3$ ) was added to 3-pentanol (31.2 mg, 0.20 mmol), the vial flushed with dry  $\text{N}_2$ , sealed, and allowed to react for 7 days at 15-20 °C, then for 18 hours at 70°C.

GC/MS (GC method C): 3 GC peaks formed after 1h, with  $t_R$  = 1138, 1160 and 1177s, corresponding to **10j** isomers (on the basis of previous experiments, with base peak of  $m/z$  338). The analysis was repeated after 1 and 4 hours, 7 days, then after 18 hours at 70°C; the relative areas of the first, second and third-eluted **10j** peaks are shown in Table 4.16.

*( $\pm$ )- $\alpha$ -methyl-2-naphthalenemethanol derivative:*

Note: alcohol (15.0 mg) not dried. Dry ethyl acetate (100  $\mu\text{l}$ ) was added to dissolve the alcohol and the mixture allowed to react at 15°C for 80 min, then at 70°C for 30 min.

GC/MS showed no products formed at 15°C, but after heating at 70°C:

GC/MS: 3 GC product peaks:

$t_R$  / s: 656 (19% total peak area) EIMS m/z: 268 ( $M^{+}$ , 97%), 149 (34), 117 (100), 104 (32), 91 (38), 78 (39), 77 (27), 61 (38).

$t_R$  /s: 1235 and 1361, (with peak area ratio 1.0 : 1.0), 2 components with indistinguishable mass spectra: (EIMS m/z: 156 (100), 155 (91), 141 (36), 154 (13), 153 (31), 128 (23), 127 (27), 77 (11)).

GC/CIMS spectrum was recorded, using *iso*-butane as reagent, but there was no ion m/z >156.

*Derivatisation of  $\alpha$ -methyl-2-naphthalenemethanol with N,O-bis(trimethylsilyl)-trifluoroacetamide (BSTFA)*

BSTFA (0.5 ml, 1.9 mmol) was added to  $\alpha$ -methyl-2-naphthalenemethanol (9 mg, 0.05 mmol), the vial flushed with dry  $N_2$ , sealed and heated at 70°C for 15 min, during which time all the solid had dissolved.

GC/MS: one product peak,  $t_R$  /s 355, EIMS: m/z 244 ( $M^{+}$ , 5%), 229 ( $[M-15]^+$ , 100%), 153 (20), 155 (17), 230 (16), 73 (87), 75 (67), 73 (87)

*Reaction of diastereoisomeric  $\alpha$ -methyl-2-naphthalenemethanol derivatives with tetrabutylammoniumfluoride*

A solution of the  $\alpha$ -methyl-2-naphthalenemethanol derivatives was divided into two portions (*ca.* 200  $\mu$ l). To one was added tetrabutylammoniumfluoride (*ca.* 100mg). After 15 h the solutions were compared by GC/MS. There was no evidence for decomposition in the vial containing tetrabutylammoniumfluoride.

*Investigation of the effect of heat on  $\alpha$ -methyl-2-naphthalenemethanol*

Two samples of  $\alpha$ -methyl-2-naphthalenemethanol (*ca.* 50 mg) was placed in vials, one with and one without ethyl acetate, flushed with N<sub>2</sub>, sealed, and heated for 1h at 130°C. GC/MS showed none of the diastereoisomeric products apparent in the reaction with chlorosilane 10.

*Preparative HPLC of ( $\pm$ )- $\alpha$ -methyl-2-naphthalenemethanol derivatives:*

The diastereoisomeric products were purified by preparative HPLC on a 250  $\times$  4.6 mm column of 5  $\mu$ m silica, with a mobile phase of dichloromethane/n-hexane (50 : 50 v/v). Five components were apparent. Two of these ( $t_R$  /min: 20.7 and 22.7), corresponded to the diastereoisomers identified by GC/MS and these fractions were collected and evaporated.

NMR of evaporated fractions:

Fraction #1:  $\delta_H$ : 1.58 (3H, d, CH<sub>3</sub>CH), 4.74 (1H, q, CHCH<sub>3</sub>), *ca.* 7.45 (3H, m, Ar), *ca.* 7.75 (4H, m, Ar).

Fraction #2:  $\delta_H$ : 1.48 (3H, d, CH<sub>3</sub>CH), 4.56 (1H, q, CHCH<sub>3</sub>), *ca.* 7.45 (3H, m, Ar), *ca.* 7.75 (4H, m, Ar).

*7.4.20 1-methyl-2,5-diphenylsilacyclopentyl 1-(1-phenethyl) ether (10a)  
– reaction of stoichiometric proportions of neat reagents.*

Neat ( $\pm$ )-phenylethanol (0.129 ml ( $d=1.011\text{gml}^{-1}$ ), 1.07 mmol) was added to 1-chloro-1-methyl-2,5-diphenyl-silacyclopentane (10) (0.305g, 1.07 mmol), stirred at 20°C for 15 min, then at *ca.* 65°C for 45 min. Analysed by GC/MS, after 5 days standing at 20°C. GC: i) temperature programme: 90 $\rightarrow$ 250°C at 10°C min<sup>-1</sup>. (GC shown in Figure 4.11): Peaks of interest:

$t_R$  / s: 531 and 543, two components with indistinguishable mass spectra; EIMS  $m/z$ : 121 (17%), 106 (16), 105 (100), 103 (11), 79 (19), 77 (30), 51 (17), 43 (11).

$t_R$  / s: 1102, 1158 and 1198, three components with relative peak areas 7.2%, 67% and 26% with indistinguishable mass spectra; EIMS  $m/z$ : 372 ( $M^+$ , 31%), 164 (26), 163 (100), 137 (35), 117 (32), 105 (85), 104 (25), 103 (28).

GC: ii) temperature programme: 60→250°C at 10°C min<sup>-1</sup>. (GC method C; GC shown in Figure 4.13): 6 peaks of interest:

$t_R$  / s: 283 (72% total peak area) EIMS  $m/z$ : 142 ( $[M+2]^+$ , 2.5%), 140 ( $M^+$ , 6%), 125 (7), 105 (100), 103 (18), 79 (20), 77 (16), 51 (15).

$t_R$  / s: 708 and 720 (6% and 7% total peak area), 2 components with indistinguishable mass spectra: EIMS  $m/z$ : 121 (21%), 106 (19), 105 (100), 79 (20), 78 (13), 77 (34), 51 (19), 43 (15).

$t_R$  / s: 1377, 1425 and 1460, (15% total peak area, 3 components with peak area ratio 5 : 66 : 29) and indistinguishable mass spectra: (EIMS  $m/z$ : 372 ( $M^+$ , 56%), 163 (100), 137 (41), 105 (88), 77 (44), 61 (38), 45 (51), 41 (37).

*GC of bis(1-phenylethyl)ether (Aldrich). (GC method C):*

$t_R$  / s: 711 and 723 (58% and 42% total peak area), 2 components with indistinguishable mass spectra: EIMS  $m/z$ : 121 (18%), 106 (22), 105 (100), 91 (14), 79 (20), 77 (37), 51 (22), 43 (15).

*Investigation into products of reaction of 1-phenylethanol:*

*Products of reaction of 1-phenylethanol with a) 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10) and b) chlorine.*

Chlorine was bubbled through neat 1-phenylethanol. The NMR spectrum of the resulting mixture was compared with that of the reaction products of 1-phenylethanol and 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10). The exact coincidence of the doublet and quartet labelled *d* and *q* in spectrum (b) was confirmed by spiking solution (b) into solution (a), as shown in Figure 7.1.

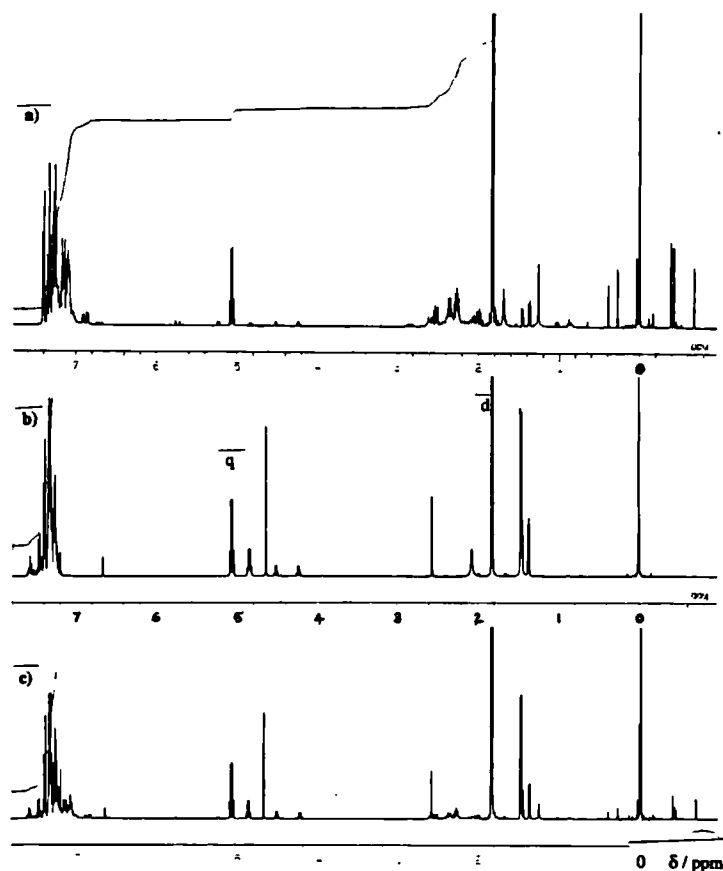


Figure 7.1 NMR spectra of the products of reaction of 1-phenylethanol: a) with 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**) and b) with chlorine. Spectrum c) solution (b) spiked into solution (a).

*Derivatisations with TMS ether of alcohols:*

*i) Preparation of ( $\pm$ )-1-phenylethoxytrimethylsilane*

N,N-Diethylaminotrimethylsilane (4.00 g, 27.5 mmol) and ( $\pm$ )-1-phenylethanol (2.24 g, 18.3 mmol) were placed in a 50 ml rb flask with 20 ml toluene and heated under reflux for 44 h. The reaction was monitored by GC/MS, which showed that the reaction was 80% complete after 17 h. and 99% complete after 44 h.

The product was distilled to produce a colourless oil (some not collected) bp 177-178°C (760mm Hg). GC/MS (normal GC conditions except T=40°C→250°C @10°min<sup>-1</sup>): eluted at 690 s., EIMS: 179 ([M-15]<sup>+</sup>, 100%), 106 (29), 105 (89). INCOS spectral library match.



$^1\text{H}$  NMR:  $\delta_{\text{H}}$ : 0.0 (9 H, s,  $\text{SiCH}_3$ ), 1.4 (3 H, d,  $\text{CH}_3$ ), 4.8 (1 H, q, CH), 7.1-7.3 (5 H, m, Ar).

ii) *Derivatisation of ( $\pm$ )-1-phenylethoxytrimethylsilane with ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane.*

( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (0.414 g, 1.45 mmol) and ( $\pm$ )-1-phenylethoxytrimethylsilane (0.279 g, 1.44 mmol) in  $\text{CDCl}_3$  (0.5 ml) were placed in an NMR tube, sealed, and allowed to react at 15-20°C.

The reaction half-life was *ca.* 19 h. After 4 d. the mixture was closely examined by GC/MS (Table 7.9) and by NMR.

Products eluted at 1394, 1443 and 1480 s, EIMS: 372 ( $\text{M}^+$ , 37%), 163 (95), 137 (37), 108 (32), 105 (100), 79 (33), 77 (40), 61 (36).

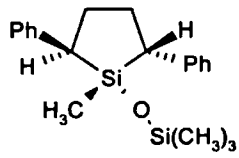
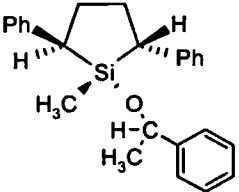
GC retention time / s.	GC relative peak area	EIMS m/z		Assignment
		$\text{M}^+$	base peak	
284	13	122	79	$\text{PhCH}(\text{CH}_3)\text{OH}$
289	6	140	105	$\text{PhCH}(\text{CH}_3)\text{Cl}$
717	1	121	105	$(\text{PhCH}(\text{CH}_3)\text{O})_2$
728	1	121	105	$(\text{PhCH}(\text{CH}_3)\text{O})_2$
1058	6	340	117	
1062	15	340	340	
1067	3	340	340	
1394	trace	372	163	
1443	25	372	163	
1480	18	372	163	

Table 7.9 GC/MS data on the products of reaction of ( $\pm$ )-1-phenylethoxy-trimethylsilane with ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane.

The NMR was complex with 9 bands between -0.4 and 0.4 ppm., the latter larger band being due to the expected product,  $(\text{CH}_3)_3\text{SiCl}$ . There were 5 doublets (1.1 to 1.8 ppm,  $\text{CH}_3\text{CH}$ ) and 5 quartets (4.5 to 5.1 ppm,  $\text{CHCH}_3$ ). GC/MS confirmed the complexity of the mixture. Vacuum distillation of the mixture led to decomposition of the desired products.

*iii) Preparation of trimethylsilyl derivative of ( $\pm$ )-1-methyl-2-phenylethanol*

N,N-Diethylaminotrimethylsilane (1.99 g, 13.7 mmol) and ( $\pm$ )-1-methyl-2-phenylethanol (1.24 g, 9.1 mmol) were placed in a 50 ml rb flask with 20 ml toluene and heated under reflux for 18 h. The reaction was monitored by GC/MS, which showed that no alcohol remained after 18 h.

The product was distilled to produce a colourless oil, 1.4 g (75% th). GC/MS: Product : alcohol ratio = 98 : 2. Product eluted at 424 s., EIMS: 193 ( $[\text{M}-15]^+$ , 26%), 118 (34), 117 (100), 75 (17), 74 (13), 73 (42), 45 (13).

$^1\text{H}$  NMR:  $\delta_{\text{H}}$ : 0.0 (9H, s,  $\text{Si}(\text{CH}_3)_3$ ), 1.2 (3H, d,  $\text{CH}_3$ ), 2.8 (2H, m,  $\text{CH}_2$ ), 4.0 (1H, m, CH), 7.2-7.4 (5H, m, Ar).

*iv) Derivatisation of ( $\pm$ )-1-methyl-2-phenylethoxytrimethylsilane with ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane.*

A solution of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (98.4 mg, 0.344 mmol in 0.5 ml  $\text{CDCl}_3$ ) was added to ( $\pm$ )-1-methyl-2-phenylethoxytrimethylsilane (73.1 mg, 0.351 mmol), the vial flushed with  $\text{N}_2$ , sealed, and allowed to react at 15-20°C.

Reaction monitoring by GC/MS, retention times (/s): starting ether, 427; chlorosilane 10, 1042, 1066 (major), 1075; products: 1601, 1634.

Isomer eluted at 1601 s, EIMS:  $m/z$  386 ( $M^+$ , 11%), 295, (24), 251 (42), 179 (38), 177 (49), 173 (22), 91 (100), 61 (34), 45 (25). Isomer eluted at 1634 s. had a very similar mass spectrum.

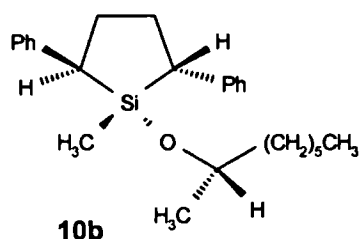
v) *Derivatisation of ( $\pm$ )-1-methyl-2-phenylethanol with ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane.*

A solution of ( $\pm$ )-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (48 mg, 0.17 mmol in 0.6 ml  $CDCl_3$ ) was added to ( $\pm$ )-1-methyl-2-phenylethanol (22 mg, 0.16 mmol), the vial flushed with  $N_2$ , sealed, and allowed to react at 15-20 °C.

Reaction monitoring by GC/MS, retention times (/s): starting alcohol, 340; chlorosilane 10, 1041, 1064 (major), 1073; products: 1552 (minor), 1596, 1629.

Isomer eluted at 1596 s, EIMS:  $m/z$  386 ( $M^+$ , 8%), 295, (19), 251 (30), 179 (31), 177 (46), 173 (19), 145 (20), 91 (100), 61 (32), 45 (24). Isomers eluted at 1552 and 1629 s. had very similar mass spectra.

#### 7.4.21 1-methyl-2,5-diphenylsilacyclopentyl-1-(2-octyl) ether (**10b**)



Chromatographically purified racemic 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (**10**) (25 mg, 0.1 mmol) in deuteriochloroform (100  $\mu$ l) was added to (+)-2-octanol (16  $\mu$ l, 0.1 mmol) and pyridine (20  $\mu$ l, 0.25 mmol) and allowed to

react at *ca.* 20°C. After 17 h the NMR spectrum and the GC/MS were recorded.

GC/MS (product mixture, GC method C): 1 major peak:

$t_R$ : 1385 s; EIMS  $m/z$ : 380 ( $[M]^+$ , 100 %), 381 (31), 268 (16), 163 (22), 117 (15), 104 (17), 91 (15), 61 (35).

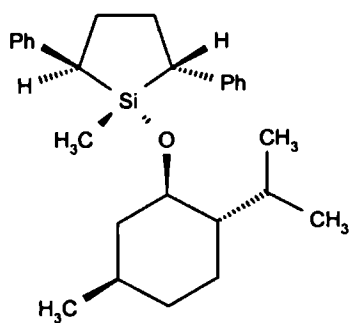
GC/MS - slow thermal gradient: 200→230°C at 1°C / min: single peak at 1229 s, no separation of diastereoisomers.

<sup>1</sup>H NMR of reaction mixture showed product formed with key signals:  $\delta_{\text{H}}$ : -0.01, 0.00 (6H, 2s, SiCH<sub>3</sub> of 2 diasts), 0.61 and 0.80 (6H, 2d, CH<sub>3</sub>CH of 2 diasts), 3.48 (2H, 2m, CH<sub>3</sub>CHCH<sub>2</sub> of 2 diasts). Other aliphatic signals were unresolved from each other.

<sup>1</sup>H-<sup>1</sup>H COSY spectrum confirmed above assignment of CH<sub>3</sub>CH signals.

HPLC: The reaction mixture was injected onto a 250 × 4.6 mm column of 5  $\mu\text{m}$  silica, with a mobile phase of dichloromethane/n-hexane (1 : 99 v/v). Two partially resolved peaks with retention time  $t_{\text{R}}$  /min: 17.6 and 18.4 were obtained, with approximate ratio 70:30.  $t_{\text{R}}$  unretained solute = 4.9 min, therefore  $\alpha$  = 1.06. Fractions from the two components were collected and analysed by GC/MS, which confirmed that they were the diastereoisomeric products, having the same GC  $t_{\text{R}}$  and EIMS as above.

#### 7.4.22 1-methyl-2,5-diphenylsilacyclopentyl-1-menthyl ether (10c)



The preparation of 10c from (1*R*, 2*S*, 5*R*)-menthol and the mixed isomers of (±)-1-chloro-1-methyl-2,5-diphenylsila-cyclopentane (10) was described above.

#### 10c: Derivatisation of (1*R*, 2*S*, 5*R*)-menthol with purified racemic 1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10)

A solution of (±)-1-chloro-1-methyl-2,5-diphenylsilacyclopentane (10), (28.6 mg, 0.1 mmol in 0.5 ml CDCl<sub>3</sub>) and pyridine (20  $\mu\text{l}$ , 0.25mmol, dried 4A mol sieve) was added to

(1*R*, 2*S*, 5*R*)-menthol (15.6 mg, 0.1 mmol), the vial flushed with dry N<sub>2</sub>, sealed, and allowed to react at 20 °C.

GC/MS (GC method C): One major GC peak formed after 24h, with  $t_R = 1452$ s, corresponding to **10c**, (on the basis of previous experiments, with base peak of  $m/z$  406), also **10c** isomer peak at 1619s (1% of peak area with respect to major product). This product was used for further purification by chromatography for NMR and other studies.

*Normal-phase HPLC separation of diastereoisomers of 10c:*

The mixture of **10c** diastereoisomers (*i.e.* prepared from racemic **10**) was injected onto a silica column with a mobile phase of CH<sub>2</sub>Cl<sub>2</sub> / *n*-hexane (5.0 % v/v), separating two components. From 20 × 20 µl repeated injections, each of 0.1 mg sample onto the column, fractions were collected corresponding to these components, having  $t_R$ : 15.4, and 17.0 min;  $\alpha = 1.24$ ;  $R_S = 1.34$ . These fractions were evaporated and analysed by GC/MS (GC method C), NMR and CD.

GC/MS:

*First-eluted diastereoisomer:* GC/MS: One GC peak:

$t_R$ : 1500 s: EIMS  $m/z$ : 407 (28), 406 ([M]<sup>+</sup>, 100 %), 268 (35), 137 (23), 117 (18), 82 (19), 81 (20), 61 (18).

*Second-eluted diastereoisomer:* GC/MS: One GC peak:

$t_R$ : 1499 s: EIMS  $m/z$ : 407 (32), 406 ([M]<sup>+</sup>, 100 %), 268 (37), 137 (22), 117 (20), 82 (16), 81 (22), 61 (17).

NMR data:

*First-eluted diastereoisomer:*  $\delta_H$ : 0.06 (3 H, s, SiCH<sub>3</sub>), 0.38 (3 H, d, CCH<sub>3</sub>), 0.62 (3 H, d, CCH<sub>3</sub>), 0.78 (3 H, d, CCH<sub>3</sub>), 1.4-2.4 (not possible to accurately integrate as impurities present in this region), 2.50 (1 H, dd, CHPh) 3.14 (1 H, dt, CHO), 7.06-7.28 (10 H, m, Ar).

*Second-eluted diastereoisomer:*  $\delta_{\text{H}}$ : 0.02 (3 H, s, SiCH<sub>3</sub>), 0.28 (1 H, ddd, CH<sub>2</sub>), 0.58 (3 H, d, CCH<sub>3</sub>), 0.60 (3 H, d, CCH<sub>3</sub>), 0.75 (1 H, m, CH<sub>2</sub>), 0.8 (1 H, m, CH<sub>2</sub>), 0.84 (1 H, m, CH<sub>2</sub>), 0.85 (3 H, d, CCH<sub>3</sub>), 0.95 (1 H, m, CH-*i-Pr*), 1.05 (1 H, m, CHCH<sub>3</sub>), 1.47 (2 H, m, CH<sub>2</sub>+CH<sub>2</sub>), 1.8 (1 H, dq, CH), 2.1 (1 H, m, CH<sub>2</sub>), 2.1 (1 H, m, CH-(CH<sub>3</sub>)<sub>2</sub>), 2.2 (1 H, m, CH-Ph), 2.3 (1 H, m, CH<sub>2</sub>), 2.3 (1 H, m, CH<sub>2</sub>), 2.58 (1 H, m, CH-Ph), 3.15 (1 H, dt, CHO), 7.07-7.29 (10 H, m, Ar).

$\delta_{\text{C}}$ : (no. of adjacent protons from DEPT) 143.85, 143.27, 128.22, 128.13, 127.27, 126.83, 124.23, 124.10 (12 CH), 73.41 (CH), 49.63 (CH), 44.24 (CH<sub>2</sub>), 38.48 (CH), 37.93 (CH), 34.20 (CH<sub>2</sub>), 31.46 (CH<sub>2</sub>), 31.31 (CH), 30.27 (CH<sub>2</sub>), 25.16 (CH), 22.64 (CH<sub>2</sub>), 21.89 (CH<sub>3</sub>), 21.12 (CH<sub>3</sub>), 15.75 (CH<sub>3</sub>), -4.02 (SiCH<sub>3</sub>).

<sup>13</sup>C-<sup>1</sup>H COSY NMR: Coupling correlations were observed between the carbon nuclei and protons at  $\delta_{\text{C}}$  and  $\delta_{\text{H}}$ /ppm: 73.41 and 3.15; 49.63 and 0.95, 44.24 and 0.28 & 0.84; 38.48 and 2.18-2.21; 37.93 and 2.58; 34.20 and 1.46-1.48; 31.46 and 2.03-2.14 & 2.30-2.36; 31.31 and 1.05; 30.27 and 1.83 & 2.30-2.36; 25.16 and 2.03-2.14; 22.64 and 1.46-1.48; 21.89 and 0.60; 21.12 and 0.85, 15.75 and 0.58; -4.02 and 0.02. Also between the aromatic signals (*i.e.* 128.22-124.10 and 7.07-7.29).

<sup>1</sup>H-<sup>1</sup>H COSY NMR: Coupling correlations were observed between the protons at  $\delta_{\text{H}}$ /ppm: 0.28 and 0.84, 1.05 and 3.15; 0.58 and 2.1; 0.60 and 1.05; 0.75 and 0.95 and 1.47; 0.8 and 1.05 and 1.47; 0.84 and 0.28; 0.85 and 2.1; 0.95 and 3.15 and 0.75; 1.05 and 0.60, 0.28; 1.47 and 0.75 and 0.8; 1.8 and 2.1, 2.3 and 2.6; 2.1 and 0.58 and 0.85; 2.1 and 2.2; 2.2 and 2.1; 2.3 and 1.8; 2.6 and 1.8; 3.15 and 0.28 and 0.95; 7.07-7.29 and 7.07-7.29.

UV and CD:

*First-eluted diastereoisomer:* UV:  $\lambda_{\text{max}}$  (CH<sub>3</sub>CN)/nm 200 and 232 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  18 100 and 7 700);

CD:  $\lambda_{\max}$  (CH<sub>3</sub>CN)/nm 194, 206 and 232 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  +11.8, -5.4, and -4.0).

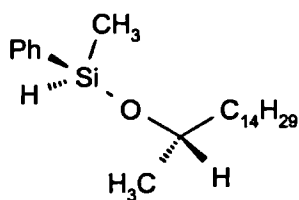
Anisotropy factor:  $g_{232} = -5.2 \times 10^{-4}$ .

*Second-eluted diastereoisomer*: UV:  $\lambda_{\max}$  (CH<sub>3</sub>CN)/nm 200 and 232 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  20 400 and 8 600);

CD:  $\lambda_{\max}$  (CH<sub>3</sub>CN)/nm 194, 205 and 233 ( $\Delta\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  -17.1, +6.0, and +4.1).

Anisotropy factor:  $g_{233} = +4.7 \times 10^{-4}$ .

#### 7.4.23 *Methylphenylsilyl 2-hexadecyl ether (1k)*



Racemic chloromethylphenylsilane (1) (45  $\mu\text{l}$ , 0.30 mmol) in deuteriochloroform (0.6 ml) was added to ( $\pm$ )-2-hexadecanol (69.3 mg, 0.29 mmol) and pyridine (120  $\mu\text{l}$ , 1.5 mmol) and allowed to react at 30°C for 5 min before running the NMR spectrum. After a

further 2 h at 25°C the GC/MS was recorded.

<sup>1</sup>H NMR of reaction mixture showed product formed:  $\delta_{\text{H}}$ : 0.44 (3H, d, SiCH<sub>3</sub> of 2 diasts), 0.88 (3H, t, CH<sub>3</sub>CH<sub>2</sub> of 2 diasts), 1.13 and 1.17 (3H, 2d, CH<sub>3</sub>CO of 2 diasts), 1.15-1.52 (26H, m, aliphatic of 2 diasts), 3.85 (1H, m, CHO of 2 diasts), 5.07 (1H, m, SiH of 2 diasts), 7.35-7.62 (5H, m, aromatic of 2 diasts)

GC/MS (product mixture, GC method B): 4 peaks;

$t_{\text{R}}$ : 498 s (21% of total peak area); EIMS:  $m/z$ : 181 (181, 35%), 180 (46), 179 (82), 166 (42), 165 (100), 121, (40), 51 (37), 43 (50). Identified as (PhSiCH<sub>3</sub>CH)<sub>2</sub>O by comparison with results from preparation of 1a.

$t_{\text{R}}$ : 543 s (55% total peak area);  $t_{\text{R}}$  and EIMS:  $m/z$  corresponding to the starting alcohol:  $t_{\text{R}}$ : 773 s and 783 s (10% and 15% total peak area); EIMS: indistinguishable spectra,  $m/z$ : 165 (83%), 147 (64), 137 (100), 121 (57), 61 (45), 55 (31), 43 (69), 41 (82).

NB. This sample solution was not fresh, which may explain the apparent hydrolysis (more starting material alcohol present here cpw the NMR ran at  $t=5$  min)

#### 7.4.24 *Attempted preparation of 1-methyl-2,5-di-(4-cyanophenyl)silacyclopentane (14)*

The preparation was set up in a similar way as for that of 6. Sodium spheres (740 mg, 32.2 mmol) were washed free of oil with THF and placed in the flask with THF (30 ml). 4-Cyanostyrene (ex- Acrös, 2.32 g, 17.9 mmol) and dichloromethylsilane (1.03 ml, 9.86 mmol) and THF (20 ml) was placed in the pressure-equalising dropping funnel. A few drops of this mixture was added to the flask at 10°C, and after 1 hour the remaining mixture added over 30 minutes, then left stirring overnight at 20°C. The mixture was sampled after 0.5, 1.5 and 18 hours and analysed by  $^1\text{H}$  NMR and GC/MS. The NMR data showed that the dichloromethylsilane concentration decreased more rapidly than that of the 4-cyanostyrene. At 1.5 hours the concentration ratio of dichloromethylsilane to 4-cyanostyrene had decreased from the initial value of 0.55 to 0.25. After 18 hours the dichloromethylsilane was undetectable. At that time there was no sign in the NMR of any of the desired product isomers, only some remaining 4-cyanostyrene (at *ca.*  $\frac{1}{8}$  the original concentration). A number of singlets in the range  $\delta_{\text{H}}$ : 0.2 - 0.6 ppm that were present after 1.5 hours were not apparent after 18 hours. At no time were there any doublets at lower chemical shift than 0.6 ppm. The GC/MS (temperature programmed to 270°C) showed only evidence for 4-cyanostyrene, with no evidence for 14 (no peak with  $m/z$  302). There was much dark precipitate present. Attempted dissolution in  $\text{DMSO-d}_6$  for NMR analysis showed:  $^1\text{H}$  bands corresponded to entrained THF and 4-cyanostyrene. Broad bands at 6.3 - 7.6 ppm and at 2.6 - 0.8 ppm were probably due to aromatics, aliphatics and  $\text{SiCH}_3$  groups in a polymeric environment.

A second experiment was carried out using freshly cut sodium chunks, which gave similar results.



7.4.25      *Attempted preparation of 1-methyl-2,5-di-(4-methoxyphenyl)silacyclopentane (15)*

These experiments were carried out in the same way as the previous section. Sodium chunks (580 mg, 25.2 mmol) were washed free of oil with THF and placed in the flask with THF (30 ml). 4-Methoxystyrene (ex-Aldrich, 2.40 g, 17.9 mmol) and dichloromethylsilane (0.93 ml, 8.9 mmol) and THF (30 ml) were placed in the pressure-equalising dropping funnel. This mixture was added to the flask at <10°C over 30 minutes, then left stirring overnight at 20°C. A precipitate, pale blue, becoming grey, started to form after 1 hour. The mixture was sampled after 1 and 3 hours and analysed by <sup>1</sup>H NMR and GC/MS. The NMR data showed that the dichloromethylsilane concentration decreased more rapidly than that of the 4-methoxystyrene. After 3 hours some 4-methoxystyrene remained, but little dichloromethylsilane. There was no sign in the NMR of any of the desired products. The GC/MS showed no molecular ion evidence for the expected product **15** (i.e. no peak in the GC gave a molecular ion at m/z 284).

The experiment was repeated with high-sodium lithium (ex-Aldrich), under similar conditions, but was equally unsuccessful.

7.4.26      *Attempted preparation of 1-methyl-2,5-di-(4-pyridyl)silacyclopentane (16) from 4-vinylpyridine and dichloromethylsilane*

THF was freshly distilled prior to use as solvent and for washing the sodium. With apparatus set up in a similar way to that for the preparation of the diphenylsilacyclopentane (**6**), sodium chunks (8.1 g, 0.35 mol) and THF (25 ml) were cooled to -40°C in a flask flushed with N<sub>2</sub>. A mixture of dichloromethylsilane (10.4 ml, 0.10 mol) and 4-vinylpyridine (21.5 ml, 0.20 mol) in THF (25 ml) was added to the stirred contents of the flask over 40 minutes at -40°C. After 20 minutes the contents became more viscous, so a

further 25 ml THF was added. After 1 hour the temperature was allowed to rise to 15-20°C and the mixture stirred overnight, monitored by  $^1\text{H}$  NMR and GC/MS. Aliquots of reaction mixture were removed under  $\text{N}_2$  and added to dry  $\text{CDCl}_3$ , then the precipitate was spun down by centrifuge. NMR showed that the  $\text{SiCH}_3$  doublet ( $\delta_{\text{H}} \approx 0.9$  ppm) of the starting material had disappeared, being replaced by broad bands at *ca.* 0.2 ppm. The vinylic proton signals of the starting material ( $\delta_{\text{H}}$  5.47 (1H, d,  $\text{CH}_2$ ), 5.95 (1H, d,  $\text{CH}_2$ ), 6.64 (1H, dd, CH)) were no longer present. While there were some sharp bands in the region associated with pyridine, most of the integral in this region (6.7-7.1 and 8.3-8.5 ppm) was due to broad bands, presumably from pyridyl groups in a polymeric environment.

There was no evidence for the expected product, there being no distinct doublet at *ca.* 0 ppm, or peak in the GC/MS with a molecular ion at  $m/z$  254. After 24 h, the grey gelatinous reaction mixture was stirred with  $\text{CH}_2\text{Cl}_2$  (100 ml) and the resulting slurry filtered to remove excess sodium and insoluble precipitate. The  $^1\text{H}$  NMR showed little difference from that noted above. Trifluoroacetic acid (TFA, 3 drops) and  $\text{D}_2\text{O}$ , (200  $\mu\text{l}$ ) was added to the NMR solution ( $\text{CDCl}_3$ ) and the resulting layers re-analysed by  $^1\text{H}$  NMR. The aqueous layer was clearly enriched in the pyridyl-containing product, with very little of the  $\text{SiCH}_3$ -containing products remaining. Aqueous ammonia was added to the aqueous layer and the product back-extracted into  $\text{CDCl}_3$ , which was then dried ( $\text{MgSO}_4$ ) and the NMR recorded again. Although still impure, the product gave signals corresponding to the pyridyl group and two aliphatic groups ( $\delta_{\text{H}}$ : *ca.* 8.5, 7.1 and 2.6, 1.7).

The  $\text{CDCl}_3$  layer contained a higher proportion of  $\text{SiCH}_3$ -containing products, giving a slightly less broad band at *ca.* 0.1 ppm. GC/MS analysis (GC method C) showed this to be mostly siloxane polymers ( $\{\text{OSiHCH}_3\}_n$ ).

GC/MS analysis of all the various extracts showed only one major peak with  $t_R=1020$  s. EIMS m/z: 213 ( $[M+H]^+$ , 39 %), 212 ( $[M]^+$ , 78%), 106, (78), 93 (100), 92 (67), 65 (86), 51 (49), 39 (87).

Many of these extracts were suspected (NMR evidence) to contain both silicon-methyl and pyridyl groups in a polymeric environment (although not necessarily in the same compound); presumably these compounds were not eluted from the GC.

In the experiments that followed, the major non-polymeric, non-silicon containing product of these reactions ( $t_R=1020$  s), was shown to be 4,4'-(1,4-butanediyl)bipyridine (17).

The reaction was repeated with the following variations in an attempt to produce the desired product:

a) the vinylpyridine was dried by storing over activated molecular sieve (4A) for one week, then refluxed for 30 minutes over NaOH pellets from which it was distilled. In this case the vinylpyridine was added to a mixture of sodium and dichloromethylsilane in THF (whereupon the metal surface lost its reddish colouration). After allowing to react overnight, an aliquot was taken and evaporated, the residue suspended in  $CDCl_3$ . This was washed with  $D_2O$  and analysed by NMR and GC/MS. The NMR was not particularly helpful, but the GC/MS showed that, apart from the coupled product 17, there was a minor (3% by peak area) component which eluted at 1150 s, with EIMS m/z: 256 ( $[M]^+$ , 14%), 151 (44), 150 (100), 148 (31), 123 (31), 106, (75), 51 (40), 45 (53), 43 (37). After further manipulation of this fraction and work up of the bulk product, this product was not detected again.

b) Sodium was prepared as a dispersion by vigorous stirring in oil above its melting point.<sup>185</sup> The vinylpyridine was dried over molecular sieve and NaOH pellets, then refluxed for 30 minutes over calcium hydride from which it was distilled. To the mixture of sodium

(washed under dry N<sub>2</sub>) and 4-vinylpyridine in THF at -30 to -60°C the dichloromethylsilane was added dropwise. Evidence for the 4-pyridyl-(CH<sub>2</sub>)<sub>4</sub>-4-pyridyl product **17**, was as seen before, *i.e.*:

GC  $t_R$  = 1024 s, EIMS  $m/z$ : 212 ([M]<sup>+</sup>, 91%), 107 (42), 106, (91), 93 (93), 92 (61), 65 (100), 51 (56), 39 (100).

However, there also appeared to be the 4-pyridyl-(CH<sub>2</sub>)<sub>3</sub>-4-pyridyl analogue:

GC  $t_R$  = 947 s, EIMS  $m/z$ : 198 ([M]<sup>+</sup>, 66%), 106, (75), 93 (100), 78 (27), 77 (29), 65 (40), 51 (33), 39 (60).

c) As above, but slow addition of 4-vinylpyridine to sodium dispersion at 20°C, which was then left stirring overnight. Dichloromethylsilane was then added to the flask.

d) 4-vinylpyridine dried as above and added together with dichloromethylsilane to stirred sodium spheres (ex-Aldrich) in THF.

In all cases a) to d) above, the major products were 4,4'-(1,4-butanediyl)bispyridine (**17**) (or the propyl analogue), and polymeric products containing SiCH<sub>3</sub> units and/or pyridyl units.

#### 7.4.27 *Attempted preparation of 1,1-dimethyl-2,5-di-(4-pyridyl)silacyclopentane (18) from 4-vinylpyridine and dichlorodimethylsilane.*

A mixture of vinylpyridine (9 ml, 83 mmol, dried as in (a) above), and dichlorodimethylsilane (5 ml, 48 mmol) was added dropwise with stirring to sodium chunks (6.0 g, 260 mmol) in dry THF (*ca.* 30 ml) and molecular sieve (*ca.* 5 g, activated at 400°C) at *ca.* 0-35°C. After 90 min the mixture became more viscous, so more THF (30 ml) was added and the mixture stirred overnight at 15-20°C. NMR analysis of aliquots of the reaction mixture and derived acid/base extracts failed to provide any SiCH<sub>3</sub> doublet which could have been evidence for the formation of the intended product.

A D<sub>2</sub>O/TFA extract of a reaction mixture aliquot analysed by GC/MS gave no peak with EIMS m/z 268, as would have been expected from **18**. The only GC peak producing ethylpyridine fragments (m/z 106) had the same retention time as 4,4'-(1,4-butanediyl)bispyridine (**17**) but with a modified EIMS:

GC  $t_R$  = 1022 s, EIMS m/z: 215 ([MH of 2 × <sup>2</sup>H product]<sup>+</sup>, 36%), 214 ([M of 2 × <sup>2</sup>H product]<sup>+</sup>, 82%), 213 ([M of 1 × <sup>2</sup>H product]<sup>+</sup>, 65%), 212 ([M of product]<sup>+</sup>, 25%), 107 (75), 106 (59), 94 (92), 93 (100), 92 (48), 66 (91), 65 (72), 52 (30), 51 (67), 40 (63), 39 (85).

A sample of the crude product was mixed with ethyl acetate. As with other solvents, the product was mostly insoluble. A clear solution was separated by centrifuge and analysed by GC/MS.

GC  $t_R$  = 1021 s, EIMS m/z: 213 ([M+H]<sup>+</sup>, 20%), 212 ([M]<sup>+</sup>, 99%), 120 (38), 106 (96), 93 (99), 92 (63), 65 (100), 51 (52), 39 (99).

GC  $t_R$  = 1215 s, EIMS m/z: 269 ([MH]<sup>+</sup>, 24%), 268 ([M]<sup>+</sup>, 100%), 267 (77), 163 (50), 106 (38), 59 (47), 51 (33), 43 (74). Also a small band at m/z 282 (6%), probably an impurity.

The bulk of the crude product was decanted from some excess sodium and molecular sieve. After partial evaporation, CH<sub>2</sub>Cl<sub>2</sub> (50 ml) and 1M HCl was added to pH 1. The aqueous layer (which contained much precipitate) was washed with CH<sub>2</sub>Cl<sub>2</sub>, then adjusted to pH 14 with aqueous ammonia. When this was shaken with CH<sub>2</sub>Cl<sub>2</sub> (40 ml), the mixture settled as three phases. Solid phase: filtered, washed with H<sub>2</sub>O (20 ml), acetone (10 ml), then dried to yield a lilac solid (1.4 g). This was insoluble in H<sub>2</sub>O, acetone, CH<sub>2</sub>Cl<sub>2</sub>, toluene, hexane, CCl<sub>4</sub>, and DMSO (cold or hot). NMR and GC/MS were therefore of little use for analysis. The compound was assumed to be polymeric and of no further interest. Organic phase: GC/MS showed the major components to be 4,4'-(1,4-butanediyl)bispyridine (**17**) with

the funnel with dry 2-methyl-2-propanol (distilled from calcium hydride, 23.8 g, 0.25 mol) and dry THF (30 ml) and added dropwise to the vigorously stirred lithium, the temperature being maintained between -10 and -30°C. The mixture was then stirred overnight at 15°C. Testing small aliquots by addition to D<sub>2</sub>O, followed by GC/MS analysis showed, as described in previous experiments, the presence of the title product, and no deuteration, indicating that protonation of the organolithium intermediate was complete. To remove excess lithium, 2-methyl-2-propanol (4.6 g, 0.06 mol) was added to the stirred mixture, and the temperature raised to 35°C. This was then extracted with a mixture of diethyl ether (150 ml) and water (50 ml). The ether layer was washed with water (50 ml), then dried (MgSO<sub>4</sub>), filtered and evaporated at 60°C to yield a yellow oil, 19.3 g (46% th.). Distillation was hampered by the ready solidification of product in the condenser. The problem was reduced by fitting the stillhead directly to the pig. A small fraction was collected by distillation (3.35 g, bp 141-142°C, 0.27 mm Hg), and analysed by NMR and GC/MS.

NMR  $\delta_{\text{H}}$ : 1.64 (4H, m, CH<sub>2</sub>), 2.58 (4H, m, CH<sub>2</sub>), 7.06 (4H, d, py), 8.45 (4H, d, py)

[*cpw lit.*<sup>187</sup> 1.64 (4H, m, CH<sub>2</sub>), 2.59 (4H, m, CH<sub>2</sub>), 6.95 (4H, d, py), 8.33 (4H, d, py)]

NMR  $\delta_{\text{C}}$ : 29.60 (CH<sub>2</sub>), 34.85 (CH<sub>2</sub>), 123.73 (pyC-3), 149.66 (pyC-2), 150.85 (pyC-4)

(<sup>1</sup>H-<sup>13</sup>C COSY correlated the above proton and carbon assignments, shown above in same order).

GC (method B): One major peak (>95% area):  $t_{\text{R}}$  = 562 s, EIMS  $m/z$ : 212 ([M]<sup>+</sup>, 95%), 120 (30), 106 (87), 93 (100), 92 (59), 65 (92), 51 (53), 39 (86).

#### 7.4.29 *Preparation of dilithiated 4,4'-(1,4-butanediyl)bispyridine and attempted silylation*

##### *i) Butyllithium as base*

some of the propyl analogue. Aqueous phase: NMR showed the presence of sharp  $\text{SiCH}_3$  bands, but at low molar ratio with respect to the pyridyl bands. The product was probably a mixture of siloxanes and 17. The latter compound was apparent from GC/MS; there was no further evidence for the cyclic target compound (18) in any analysis of these extracts.

The preparation was repeated with minor modifications. The vinylpyridine was refluxed from calcium hydride and sodium spheres were used. After 24 h, aliquots (ca. 200  $\mu\text{l}$ ) of the reaction mixture were added to each of three vials containing 100  $\mu\text{l}$  of a)  $\text{D}_2\text{O}$ , b)  $\text{H}_2\text{O}$ , c)  $(\text{CH}_3)_2\text{SiCl}_2$  and d)  $(\text{CH}_3)_3\text{SiCl}$ . The contents were mixed by shaking, then extracted with ethyl acetate (1 ml), for analysis by GC/MS. The first two gave product peaks with identical retention time and had molecular ions with  $m/z$  214 and 212 and spectra similar to those noted above for  $\text{PyCHD}(\text{CH}_2)_2\text{CHDPy}$  and  $\text{Py}(\text{CH}_2)_4\text{Py}$  respectively. The other two gave GC/MS which probably corresponded only to siloxanes (formed on extraction): c) gave no product with  $m/z$  268; only siloxane by-products obtained. d) gave no product with  $m/z$  284 or 356.

The solution from a) was extracted from aqueous solution (basified with ammonia) into  $\text{CH}_2\text{Cl}_2$ , then extracted back into aqueous acid (HCl). GC/MS analysis at each stage showed that the molecular ion was at  $m/z$  214 throughout.

#### 7.4.28 Preparation of 4,4'-(1,4-butanediyl)bispyridine (17)

A 3-necked flask was set up with overhead stirrer, pressure-equalising dropping funnel, and PTFE tubes for dry  $\text{N}_2$  purge and washing/sampling. A lithium dispersion (9.0 g  $\times$  30% in oil, 2.7 g Li, 0.39 mol) and dry THF (20 ml), was run into the flask and vigorously stirred, then allowed to settle and the solution displaced from under the suspended lithium by nitrogen pressure. After 2 similar washes more THF (70 ml) was added to the flask, which was cooled to  $-20^\circ\text{C}$ . 4-Vinylpyridine (distilled from calcium hydride, 21.5 ml, 0.20 mol) was placed in

Distilled 4,4'-(1,4-butanediyl)bispyridine (17) (2.1 g, 10 mmol), and THF (50 ml) were placed in a single-necked flask fitted with a magnetic stirrer, Subaseal and nitrogen purge. After cooling to  $-78^{\circ}\text{C}$  (precipitation occurred), *n*-butyllithium (8 ml  $\times$  2.5 M solution in hexanes, 20 mmol) was added with stirring by syringe over 30 minutes. The orange mixture became wine-red as the temperature was allowed to rise to  $10^{\circ}\text{C}$  over 2 hours. An aliquot (2-3 drops) was removed and added to  $\text{D}_2\text{O}$  (100  $\mu\text{l}$ ), instantly losing its colour. Products were extracted into ethyl acetate and analysed by GC/MS. 4 components were apparent:

$t_{\text{R}}$ : 663 s (14% area), EIMS  $m/z$ : 269 (6%), 254 (13), 253 (17), 240 (34), 228 (55), 227 (100), 226 (75), 120 (52), 107 (61), 93 (47), 39 (62).

$t_{\text{R}}$ : 822 s (5% area), EIMS  $m/z$ : 330 ( $[\text{M}]^{+\cdot}$ , 7%), 274 (90), 273 (100), 272 (55), 107 (20), 41 (27). Many bands complicated by higher isotopes.

$t_{\text{R}}$ : 833 s (47% area), EIMS  $m/z$ : 326, (7%), 325 (10), 324 (7), (all  $[\text{MH}]^{+\cdot}$   $[\text{M}]^{+\cdot}$  and isotopes?), 296 (27), 295 (30), 283 (38), 282 (31), 255 (47), 254 (90), 253 (100), 147 (9), 133 (22), 119 (29), 107 (39), 39 (25).

$t_{\text{R}}$ : 838 s (34% area), EIMS  $m/z$ : 332 (12%), 331 (24), 330 (15), 329 (22), 274 (37), 273 (100), 272 (82), 271 (42), 246 (23), 245 (26), 150 (34), 149 (43), 41 (51), 39 (34).

Dichloromethylsilane (1.04 ml, 10 mmol) was added by syringe over 1 h to the mixture at  $-78^{\circ}\text{C}$ , which became orange-yellow. The temperature was allowed to rise to  $20^{\circ}\text{C}$  and the mixture stirred overnight. The reaction mixture was quenched with water, the ether layer that formed was dried and analysed by GC/MS. There were 4 peaks, similar to those seen in the  $\text{D}_2\text{O}$  test prior to the addition of dichloromethylsilane.

$t_{\text{R}}$ : 663 s: EIMS  $m/z$ : 269 (5%), 253 (11), 240 (17), 239 (23), 228 (9), 227 (50), 226 (100), 120 (45), 107 (46), 106 (28), 93 (39), 39 (45).



The later-running 3 components ( $t_R$ /s: 818, 828, 833), were in the same ratio as before and had similar EIMS except that the first and third components had none of the higher  $m/z$  ions associated with deuterium.

ii) *Lithium di-iso-propylamide (LDA) as base*

4,4'-(1,4-Butanediyl)bipyridine (63 mg, 0.30 mmol), was placed under nitrogen in a 50 ml round bottom flask with THF (20 ml) and fitted with a magnetic stirrer and Subaseal. After stirring at 20°C to dissolve, the flask was cooled to -78°C and LDA solution (1.0 ml, 2.0 mmol) added over 5 min, then stirred for a further 30 min. The temperature was raised to 20°C. Aliquots were removed and added to either D<sub>2</sub>O or chlorotrimethylsilane, then extracted and analysed by GC/MS (Method B). From the D<sub>2</sub>O test: 3 GC peaks:

$t_R$ : 491 s: EIMS  $m/z$ : 210 ( $[M]^{+}$ , 39%), 106 (58), 105 (100), 92 (48), 91 (84), 79 (36), 77 (44), 65 (35). The second peak was an isomer and had 30% peak area with respect to the first.

$t_R$ : 507 s: EIMS  $m/z$ : 210 ( $[M]^{+}$ , 26%), 104 (15), 92 (38), 91 (100), 77 (10), 65 (30), 51 (9), 39 (17).

$t_R$ : 569 s: EIMS  $m/z$ : 214, 213, 212 ( $[M]^{+}$  of 4,4'-(1,4-butanediyl)bipyridine (17), 3 isotopic isomers in ratio 2 : 10 : 5. Remaining spectrum corresponded to this mixture (as per previous samples).

From the (CH<sub>3</sub>)<sub>3</sub>SiCl test: GC peaks as above, but also:

$t_R$ : 565 s: EIMS  $m/z$ : 252 ( $[M]^{+}$ , 100%), 147 (23), 130 (20), 117 (88), 105 (32), 104 (35), 91 (35), 78 (32), 43 (53).

The experiment was repeated using a freshly opened batch of LDA. Using the same procedure, LDA solution (0.62 ml, 1.24 mmol) was added to 4,4'-(1,4-butanediyl)bipyridine (17) (132 mg, 0.62 mmol). After stirring at -78°C for 30 min, an aliquot was removed (by

syringe, as normal) and added to D<sub>2</sub>O. GC/MS analysis of the extracted product showed that little dilithiation had occurred, and that the major product was the monolithium derivative of **17**. There was a small amount (2%) of the two coupled products from ethylbenzene (retention times and EIMS as in previous experiment). The reaction mixture temperature was raised to 20°C and left stirring for 15 h. A further aliquot was removed and added to D<sub>2</sub>O, extracted and analysed by GC/MS (Method B).

The major product was clearly the dilithiated **17**, ([M]<sup>++</sup> at m/z 214). The extract was dried (MgSO<sub>4</sub>) and analysed by NMR.

<sup>1</sup>H NMR: as reported for non-deuterated analogue **17**, above. CHD broad.

<sup>13</sup>C NMR: δ<sub>C</sub>: 29.62 (C-2 and C-3); 34.41, 34.61, 34.81, (triplet, CHD-1 and CHD-4), 34.97 (C-1 and C-4 of non-deuterated impurity?), 123.58, 149.71, 150.92 (aromatic).

Aliquots (100 μl) of this reaction mixture (brown coloration throughout the procedure) were transferred to pre-dried vials, and one drop of each of the following was added:- (CH<sub>3</sub>)<sub>3</sub>SiCl, (CH<sub>3</sub>)<sub>2</sub>SiCl<sub>2</sub>, CH<sub>3</sub>SiHCl, and D<sub>2</sub>O. In each case, the colour instantly changed to deep yellow, which became less intense with time. Some precipitation occurred with the chlorosilanes. Each mixture was extracted with ethyl acetate and analysed by GC/MS. In each case siloxanes were apparent, running early in the GC. Other GC/MS data:

Products from reaction with (CH<sub>3</sub>)<sub>3</sub>SiCl were left for 15 h at 20°C before adding D<sub>2</sub>O and extracting: GC/MS run twice. First run, rather overloaded: 5 GC peaks:

*t<sub>R</sub>* = 190 s, (5 % total peak area), EIMS m/z: 221 ([M-15]<sup>+</sup>, 100%), 73 (53) *etc.*  
(CH<sub>3</sub>)<sub>3</sub>SiOSi(CH<sub>3</sub>)<sub>2</sub>OSi(CH<sub>3</sub>)<sub>3</sub>.

*t<sub>R</sub>* = 276 s, (5 % total peak area), EIMS m/z: 155 (6%), 140 (82), 86 (63), 44 (100) *etc.*

Unrelated product.

$t_R$  = 564 s, (59 % total peak area), EIMS corresponding to 4,4'-(1,4-butanediyl)bispyridine (non-deuterated).

$t_R$  = 607 s, (19 % total peak area), EIMS m/z: 373 (3%), 301 (7), 300 (10), 285 (9), 272 (40), 180 (83), 165 (29), 73 (100), 45 (30).

$t_R$  = 657 s, (10 % total peak area), EIMS m/z: 374 ( $[M]^{+?}$ , 10%), 359 (9), 346 (16), 254 (100), 211 (48), 147 (63), 73 (40).

GC/MS re-run after 40 min: peaks at 607 and 657 s no longer present.

Products from reaction with  $(CH_3)_2SiCl_2$ : no new peaks eluting later in the GC than the starting material, and no evidence for the expected product, **18**, (*i.e.* no compound with a molecular ion with m/z 268).

Products from reaction with  $CH_3SiHCl_2$ , no new peaks eluting later in the GC than the starting material, and no evidence for the expected bispyridyl analogue of **6** (*i.e.* no compound with a molecular ion with m/z 254).

The products from the reaction with  $D_2O$  confirmed that the dilithiated intermediate was still the major compound and that this procedure was a valid means of testing its reaction with a variety of reagents.

Chlorotrimethylsilane (80  $\mu$ l, 0.62 mmol) was added to the remaining reaction mixture at  $-78^\circ\text{C}$ . The mixture remained brown while the temperature was raised to  $20^\circ\text{C}$  and was left at this temperature overnight. A sample was removed, basified, extracted into ethyl acetate and analysed by GC (method B): Three major peaks:

$t_R$  = 623 s, EIMS m/z: 358 ( $[M]^{+?}$ , 0.9%), 357 (1.2), 180 (10), 179 (40), 178 (100), 73 (79), 65 (8), 45 (26), 43 (13), 39 (9).

$t_R = 673$  s, EIMS m/z: 429 ( $[M]^+$ , 1.2 %), 358 (0.1), 357 (0.3), 341 (2), 251 (3), 180 (6), 179 (19), 178 (100), 106 (6), 73 (92), 59 (5), 45 (32), 43 (13), 39 (9).

$t_R = 680$  s, EIMS m/z: 429 ( $[M]^+$ , 1.5 %), 358 (0.2), 357 (0.3), 356 (0.2), 341 (1), 251 (4), 180 (6), 179 (22), 178 (100), 74 (6), 73 (78), 45 (31), 43 (11).

The reaction mixture flask was fitted with a condenser and gently heated to reflux for 30 minutes. As the temperature rose, the solution changed colour from brown to pale orange. The solvent was evaporated at 30°C under reduced pressure. The residue was shaken with H<sub>2</sub>O (20 ml) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml) (pH of aqueous layer was 11.9). The organic layer was separated, dried (MgSO<sub>4</sub>), and evaporated at 60°C under reduced pressure. The product was analysed by GC/MS and NMR. GC (method B, but run at unusually high concentration): Three major peaks, with shorter retention times than those above (GC injector liner changed), but similar EIMS in the regions of low concentration. EIMS not shown. In regions of high concentration, self-CIMS occurred:

$t_R = 593$  s, CIMS m/z: 358 (49), 357 ( $[MH]^+$ , 100), 356 (12), 286 (13), 285 (37), 180 (11), 179 (20), 178 (28).

$t_R = 643$  s, CIMS m/z: 431 (14), 430 (48), 429 ( $[MH]^+$ , 100), 428 (16), 357 (10), 251 (9) 180 (9), 179 (12), 178 (25), 45 (18).

$t_R = 649$  s, CIMS m/z: 431 (12), 430 (28), 429 ( $[MH]^+$ , 100), 357 (8), 341 (11), 180 (15), 179 (27), 178 (50), 74 (11), 73 (44), 45 (39).

The product was re-analysed by GC/MS. (GC method B, normal concentration): Three major peaks, with retention times as those above and with spectra similar to those above in regions of low concentration, *i.e.* when EIMS occurred as normal:

$t_R = 590$  s, EIMS  $m/z$ : 179 (25), 178 (100), 73 (87), 65 (9), 59 (9), 51 (8), 45 (21), 43 (10), 39 (7).

$t_R = 639$  s, EIMS  $m/z$ : 180 (6), 179 (16), 178 (100), 106 (4), 74 (7), 73 (85), 45 (26), 43 (9).

$t_R = 645$  s, EIMS  $m/z$ : 251 (5), 180 (3), 179 (16), 178 (100), 74 (6), 73 (84), 45 (28), 43 (12).

Using the same procedure, a solution of 4,4'-(1,4-butanediyl)bispypyridine (**17**) (229 mg, 1.08 mmol) was prepared and cooled to  $-78^\circ\text{C}$  (in this case the starting material did not precipitate from solution). LDA solution (1.08 ml, 2.16 mmol) was added steadily over 5 minutes to the stirred solution. Testing the reaction mixture as before, ( $\text{D}_2\text{O}$  test) showed that after 2 hours (orange colour) compound **17** was 20% monolithiated and 0% dilithiated; after a further 0.5 hours (deep orange colour) it was 38% monolithiated and 7% dilithiated. After raising the temperature to  $5^\circ\text{C}$  over 1.5 hours and holding at  $5^\circ\text{C}$  for a further 0.8 hours, there was 50% monolithiated and 30% dilithiated compound **17**. The reaction mixture temperature was reduced to  $-78^\circ\text{C}$  and dichlorodimethylsilane (150  $\mu\text{l}$ , 1.24 mmol), was added by syringe. The mixture remained as a red-brown suspension. After 15 minutes, the reaction mixture was sampled again, (100  $\mu\text{l}$  added to 200  $\mu\text{l}$   $\text{D}_2\text{O}$ , left for 3 minutes, 1 drop c.  $\text{NH}_4\text{OH}$  added, extracted with 1 ml ethyl acetate) and analysed by GC/MS. There were no new later-running compounds and compound **17** was 50% monolithiated and 20% dilithiated. The temperature was allowed to rise (over 30 minutes) to  $20^\circ\text{C}$  and the  $\text{D}_2\text{O}$  test repeated. The isotopic isomer ratio of **17** was unchanged. A second portion of dichlorodimethylsilane (5 ml, 4.1 mmol) was added to the reaction mixture at  $-78^\circ\text{C}$ . The  $\text{D}_2\text{O}$  test was repeated, showing that monolithiated and 20% dilithiated **17** was still present. There were also two small new peaks in the GC/MS:

$t_R = 649$  s, EIMS  $m/z$ : 121 (7%), 107 (16), 106 (100), 92 (9), 79 (8), 78 (39), 65 (15), 51 (39), 50 (12), 39 (16).

$t_R = 702$  s, EIMS  $m/z$ : 123 (21%), 108 (29), 106 (57), 94 (49), 93 (100), 81 (35), 80 (96), 65 (29), 51 (52), 39 (34).

The reaction mixture was refluxed for 2 hours and tested again, but showed no significant change. The reaction mixture was evaporated, dissolved in diethyl ether (30 ml) and water (50 ml) was added and the pH adjusted to 9.0 with c.  $\text{NH}_4\text{OH}$ . The organic layer was extracted, dried ( $\text{Mg SO}_4$ ) and evaporated to yield a brown oil, 0.32 g. Analysis by GC/MS gave evidence for earlier-running siloxanes (base peak having  $m/z$  73) a little **17**, and two small peaks at  $t_R$  652 and 704 s, as above.

This preparation was repeated with a similar procedure but on 3  $\times$  scale (3.35 mmol **17** in 25 ml THF, 7.2 mmol LDA, 3.35 mmol  $(\text{CH}_3)_2\text{SiCl}_2$ ). A higher temperature was used ( $0^\circ\text{C}$ , **17** precipitated out from solution). LDA was added to **17** at  $0^\circ\text{C}$  and stirred at this temperature for 5 hours, while the lithiation was monitored by the  $\text{D}_2\text{O}$  test as before. During this time the solution/suspension colour changed to orange, then deep red, yellow/green, brown and finally yellow. Aliquots of the reaction mixture were added on the usual test scale (100  $\mu\text{l}$ ) at  $20^\circ\text{C}$  to  $\text{D}_2\text{O}$ , and at  $-78^\circ\text{C}$ , to  $(\text{CH}_3)_2\text{SiCl}_2$ , or  $(\text{CH}_3\text{CH}_2)_2\text{NSi}(\text{CH}_3)_3$ . Following extraction, the  $\text{D}_2\text{O}$  test showed the ratio of the molecular ions for **17** with  $m/z$  212, 213 and 214 to be 12 : 35 : 53 (a test after 1 hour also showed the ion with  $m/z$  214 to be predominant). The chlorosilane test samples were only quenched with  $\text{D}_2\text{O}$  after 20 hours, then extracted and analysed by GC/MS. The  $(\text{CH}_3)_2\text{SiCl}_2$  sample gave no GC peak with  $t_R = 770$  s or with EIMS molecular ion at  $m/z$  268. The  $(\text{CH}_3\text{CH}_2)_2\text{NSi}(\text{CH}_3)_3$  sample gave no GC peak with fragments with  $m/z$  178.

The  $(\text{CH}_3)_2\text{SiCl}_2$  (3.35mmol, noted above) was added to the remaining bulk reaction mixture at  $-78^\circ\text{C}$  and the GC/MS checked after 30 minutes (100  $\mu\text{l}$  reaction mixture added to 200  $\mu\text{l}$   $\text{D}_2\text{O}$ , left for 3 minutes, extracted with 1 ml ethyl acetate). A new component running later than the starting material had an EIMS previously seen, believed to be **18**. GC/MS (Method

B):  $t_R$ : 769 s, (15% peak area relative to **17** (total isotopic isomers)), EIMS  $m/z$ : 269 ( $[MH]^+$ , 30%), 268 ( $[M]^{++}$ , 100), 267 (83), 163 (61), 106 (42), 59 (72), 51 (32), 43 (82). The ratio of the molecular ions for **17** (isotopic isomers) with  $m/z$  212, 213 and 214 was 10 : 35 : 55. The temperature was allowed to rise to 20°C. After 15 minutes at this temperature the colour had changed from yellow-brown to a transparent pale orange-brown, with a dark brown tarry lump at the bottom of the flask. The reaction mixture was sampled again ( $D_2O$  test repeated), showing that there was only 25% of the relative concentration of **18** with  $t_R = 769$  s (relative to the ethylbenzene peak). The flask was sealed and left overnight at -20°C, then allowed to rise to 20°C. The  $D_2O$  test was repeated, showing the complete loss of the suspected compound **18** with  $t_R = 769$  s. There was no component in the GC/MS with  $m/z$  268. The solution that had given the first positive indication of this compound in this experiment was re-analysed, but this too had decomposed. After 23 hours the reaction mixture was sampled again, to include some of the brown tar; GC/MS showed that some **18** was still present. An oven-dried pipette was used to sample the brown tar, which was added to  $D_2O$  and analysed to show no **18**. THF was added to the flask and the contents refluxed for 60 hours. Analysis of the resulting supernatant ( $D_2O$  test) showed no **18**, and still a high concentration of deuterated **17**. The THF was boiled off (temperature of the mixture allowed to reach 130°C), then *o*-xylene (refluxed over and distilled from sodium) added and the mixture heated to dissolve the viscous brown residue. Sampled for  $D_2O$  test; 2 major peaks in the GC/MS, **17** (monolithiated species predominant) and **18** (85% peak area with respect to **17**). The *o*-xylene solution was refluxed for 15 minutes, then sampled and analysed as before. The ratio of **18/17** had dropped (to *ca.* 0.25:1) and the concentration of nonlithiated **17** had increased. The ethyl acetate layer used for the GC/MS analysis was checked again after 20 minutes to confirm the presence of **18**, but when this solution was re-run after 15 hours at 20°C **18** was lost. The product was sealed and left overnight, after which time two definite layers had

formed (upper layer had 4 × volume and was clear and pale orange-brown, lower was opaque and dark brown). The product to starting material ratio was *ca.* 4 × higher in the upper layer. The layers were separated. Solvent was removed from the upper layer at 80°C at *ca.* 5 mm Hg, with great difficulty, due to bumping. The rate of evaporation reduced when there was *ca.* 5 ml of orange, fairly mobile liquid left. GC/MS showed ratio of 18/17 had increased (to *ca.* 1.3:1). Precipitation occurred on addition of diethyl ether. The orange precipitate and supernatant were separated, and the latter evaporated to *ca.* 5 ml of mobile orange liquid. The 18/17 ratio in the liquid fraction was 0.05:1. Analysis by <sup>1</sup>H NMR showed no NH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub> (no doublet at 1.0 or 1.5 ppm), *ca.* 5 moles *o*-xylene remained, also δ<sub>H</sub>: 8.7 (4H, m, pyridyl), 7.2, (4H, m, pyridyl), 2.8 (2H, m, aliphatic), 1.8 (2H, m, aliphatic), (other aliphatics inc. solvent, 2.0 → 1.0 ppm and minor SiCH<sub>3</sub> groups 0.5 → 0.1 ppm).

<sup>29</sup>Si NMR: δ<sub>Si</sub>: 8.79 (med), 4.62 (weak), 3.96 ( weak), -21.65 (med/str).

The orange precipitate was triturated with ethyl acetate. The resulting solution had a low (<0.05:1) 18/17 ratio. Portions of the precipitate were extracted with ethyl acetate / water mixtures, neutral or basified, but the resulting solutions also had low (<0.05:1) 18/17 ratios.

The lower (dark brown) of the two layers was retained. A sample of this was dissolved in ethyl acetate and washed with water. The ethyl acetate layer was analysed by GC/MS, showing the 18/17 ratio to be 0.6:1. The analysis was repeated on the same solution after 4 h; the 18/17 ratio was 0.2:1. Relative to the peak area of ethylbenzene (taken as constant), the area of 17 had risen (by 20%), while the area of 18 had fallen (by 50%).

Freshly distilled diethyl ether (10 ml) was added to this remaining reaction mixture, stirred, some precipitate allowed to settle, and the supernatant transferred to an oven-dried vial. GC/MS showed that the 18/17 ratio was 0.4:1. The solvent was removed *in vacuo* at 20°C. Dried CDCl<sub>3</sub> was added to the sample, which was analysed by GC/MS: 17 was present, but



only a trace of **18**. Comparison of peak areas in the GC/MS showed that again the decrease of concentration of **18** was accompanied by an increase of concentration of **17**. There was no sign of other decomposition products.

*7.4.30 Larger scale attempted preparation of 1-methyl-2,5-di-(4-pyridyl)-silacyclopentane (16) from 4,4'-(1,4-butanediyl)bispypyridine (17)*

Using the same procedure, a solution of 4,4'-(1,4-butanediyl)bispypyridine (**17**) (420 mg, 1.98 mmol) was dissolved in dry THF (25 ml) in a 100 ml flask with Subaseal, magnetic stirrer and N<sub>2</sub> purge and cooled to 0°C (in this case the starting material did not precipitate from solution). LDA solution (2.0 ml, 4.0 mmol) was added steadily over 20 minutes to the stirred solution at 0°C, during which time the reaction mixture became a red solution, then a deep red suspension. After 2 hours the temperature was raised to 15°C and the reaction mixture was tested as before, (D<sub>2</sub>O test) which showed that **17** was 23% monolithiated and 70% dilithiated.

The temperature was reduced to -78°C and dichloromethylsilane (206 µl, 1.98 mmol), was added by syringe over 10 minutes. After 15 minutes the temperature was allowed to rise to 0°C and the reaction mixture was analysed again, (D<sub>2</sub>O test) which showed that the predominant derivative of **17** was the bisdeuterated compound. There were no components eluting later in the GC and no compounds with the molecular ion expected from **16** (m/z 254).

The mixture was refluxed overnight, then analysed by GC/MS, but the reaction mixture was not quenched; an aliquot was diluted with dry THF in oven-dried glassware for the GC/MS analysis. Starting material, **17**, was apparent in the chromatogram, as were the typical minor impurities from the reagents, but no new peaks. An aliquot of the reaction mixture was also subjected to the usual D<sub>2</sub>O test. The amount of non-deuterated **17** was approximately equal to

the sum of the monodeuterated and bisdeuterated **17**. Under anhydrous conditions (oil pump), THF was evaporated at < 20°C and dried under high vacuum to yield a pale brown solid. This was sampled for NMR and GC/MS.

NMR: (sample not completely soluble in CDCl<sub>3</sub>)  $\delta_H$ : 8.5 (4H, d, C-2 of pyridyl), 7.3 (*ca.* 0.5 H, d, C-3 of pyridyl), 7.2 (*ca.* 1.1 H, d, C-3 of pyridyl), 7.1 (*ca.* 1.3 H, d, C-3 of pyridyl), 5.4 (0.3H, s? (br)), 4.7-4.6 (weak, aliphatic), 2.6 (2.6H, m, CH<sub>2</sub>adj. pyridyl group in **17**, but more complex pattern), 1.7-1.6 (*ca.* 1.7H, m, CH<sub>2</sub> (C-2/3 of chain)), 1.3-1.2 (4.2H, 2d?), 1.05 (1.9H, d, (CH<sub>3</sub>)<sub>2</sub>CH?), 0.1 (0.9H, s, SiCH<sub>3</sub>)

Note: Impurities made quantification difficult. C-3 signals were genuine and may reflect ring substitution. Signals assigned as C-3 did not total the expected 4H with respect to those of C-2, but some C-2 signal not integrated (isomers/related impurities?). Doublet at 1.05 ppm was at lower shift with respect to that expected for di-*iso*-propylamide ion (possibly di-*iso*-propylamine?)

GC/MS: No significant change from previous analysis.

*o*-Xylene was refluxed over, and distilled from sodium, directly into the product mixture flask. The contents were refluxed for 5 minutes, then analysed by GC/MS. There was no apparent change. The mixture was allowed to stand at 20°C for 3 days, re-analysed, then refluxed for a further 4 hours and analysed again. The only change that had occurred was that **17** appeared as the non-deuterated species.

#### 7.4.31 *Attempted preparation of 16 - NMR tube experiment*

The previous experiment was repeated on a 1/10 scale in an NMR tube. **17** (45 mg, 0.21 mmol) was dissolved in THF-d<sub>8</sub> (1g) and <sup>1</sup>H and <sup>13</sup>C spectra recorded. LDA (214  $\mu$ l  $\times$  2.0 M, 0.43 mmol) was added by syringe at 20°C. The solution turned red and precipitate was immediately formed. After 1 hour some greenish / brown precipitate was present. The NMR

spectra were re-recorded and the GC/MS recorded ( $D_2O$  test). Dichloromethylsilane (22  $\mu$ l, 0.21 mmol) was added to the NMR tube and the contents mixed. The resulting solution was orange. The  $^{29}Si$  and  $^1H$  spectra and the GC/MS were recorded. The GC/MS spectra were similar to each other, with no sign of new peaks and certainly no compounds with a molecular ion with  $m/z$  254 which might correspond to 16. The  $^1H$  NMR spectrum was complicated by the presence of heptane and ethylbenzene. However, there was no evidence for a  $SiCH_3H$  doublet and the pyridyl C-2 at 8.4ppm appeared as a multiplet. The  $^{29}Si$  spectrum contained a number of bands:  $\delta_{Si}$ : 16.3 (weak); 10.3; 0.0 (TMS ref.); -13.0 (strong); -13.8 (weak); -18.7 ppm.

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